

group, halogen-substituted or unsubstituted C1-6 alkyl group, halogen-substituted or unsubstituted C1-6 alkoxy group, piperazinyl group which may have a C1-6 alkyl group as a substituent on the piperazin ring and

5 morpholino group) includes a phenylcarbamoyl group (which may be substituted on the phenyl ring by 1 to 3 groups selected from a group consisting of a halogen atom, amino group which may have 1 to 2 C1-6 alkyl groups as a substituent, carboxyl group, C1-6

10 alkoxycarbonyl group, halogen-substituted or unsubstituted C1-6 alkyl group, halogen-substituted or unsubstituted C1-6 alkoxy group, piperazinyl group which may have 1 to 3 C1-6 alkyl groups as a substituent on the piperazin ring and morpholino group, and an

15 amino group moiety may be substituted by another C1-6 alkyl group or phenyl C1-6 alkyl group), for example, a phenylcarbamoyl group, 2-fluorophenylcarbamoyl group, 3-fluorophenylcarbamoyl group, 4-fluorophenylcarbamoyl group, 2-chlorophenylcarbamoyl group, 3-

20 chlorophenylcarbamoyl group, 4-chlorophenylcarbamoyl group, 2-bromophenylcarbamoyl group, 3-bromophenylcarbamoyl group, 4-bromophenylcarbamoyl group, 2-iodophenylcarbamoyl group, 3-iodophenylcarbamoyl group, 4-iodophenylcarbamoyl group, 2,3-

25 difluorophenylcarbamoyl group, 3,4-difluorophenylcarbamoyl group, 3,5-difluorophenylcarbamoyl group, 2,4-difluorophenylcarbamoyl group, 2,6-difluorophenylcarbamoyl group, 2,3-dichlorophenylcarbamoyl group,

3,4-dichlorophenylcarbamoyl group, 3,5-dichlorophenyl-
 carbamoyl group, 2,4-dichlorophenylcarbamoyl group,
 2,6-dichlorophenylcarbamoyl group, 3,4,5-trifluoro-
 phenylcarbamoyl group, 2,3-difluorophenylcarbamoyl
 5 group, 3,4,5-trichlorophenylcarbamoyl group, 2,4,6-
 trifluorophenylcarbamoyl group, 2,4,6-trichlorophenyl-
 carbamoyl group, 2-methylphenylcarbamoyl group, 3-
 methylphenylcarbamoyl group, 4-methylphenylcarbamoyl
 group, 2-methyl-3-chlorophenylcarbamoyl group, 3-
 10 methyl-4-chlorophenylcarbamoyl group, 2-chloro-4-
 methylphenylcarbamoyl group, 2-methyl-3-fluorophenyl-
 carbamoyl group, 2-trifluoromethylphenylcarbamoyl
 group, 3-trifluoromethylphenylcarbamoyl group, 4-
 trifluoromethylphenylcarbamoyl group, N-methyl-N-
 15 phenylcarbamoyl group, N-(2-fluorophenyl)-N-
 methylcarbamoyl group, N-(3-fluorophenyl)-N-
 methylcarbamoyl group, N-(4-fluorophenyl)-N-
 methylcarbamoyl group, N-(2-chlorophenyl)-N-
 methylcarbamoyl group, N-(3-chlorophenyl)-N-methyl-
 20 carbamoyl group, N-(4-chlorophenyl)-N-methylcarbamoyl
 group, N-(4-bromophenyl)-N-methylcarbamoyl group, N-(2-
 iodophenyl)-N-methylcarbamoyl group, N-(3-iodophenyl)-
 N-methylcarbamoyl group, N-(4-iodophenyl)-N-methyl-
 carbamoyl group, N-(2,3-difluorophenyl)-N-methyl-
 25 carbamoyl group, N-(3,4-difluorophenyl)-N-methyl-
 carbamoyl group, N-(3,5-difluorophenyl)-N-methyl-
 carbamoyl group, N-(2,4-difluorophenyl)-N-methyl-
 carbamoyl group, N-(2,6-difluorophenyl)-N-methyl-

- carbamoyl group, N-(2,3-dichlorophenyl)-N-methyl-
 carbamoyl group, N-(3,4-dichlorophenyl)-N-methyl-
 carbamoyl group, N-(3,5-dichlorophenyl)-N-methyl-
 carbamoyl group, N-(2,4-dichlorophenyl)-N-methyl-
 5 carbamoyl group, N-(2,6-dichlorophenyl)-N-methyl-
 carbamoyl group, N-(3,4,5-trifluorophenyl)-N-methyl-
 carbamoyl group, N-(3,4,5-trichlorophenyl)-N-methyl-
 carbamoyl group, N-(2,4,6-trifluorophenyl)-N-methyl-
 carbamoyl group, N-(2,4,6-trichlorophenyl)-N-methyl-
 10 carbamoyl group, N-(2-methylphenyl)-N-methylcarbamoyl
 group, N-(3-methylphenyl)-N-methylcarbamoyl group, N-
 (4-methylphenyl)-N-methylcarbamoyl group, N-(2-methyl-
 3-chlorophenyl)-N-methylcarbamoyl group, N-(3-methyl-4-
 chlorophenyl)-N-methylcarbamoyl group, N-(2-chloro-4-
 15 methylphenyl)-N-methylcarbamoyl group, N-(2-methyl-3-
 fluorophenyl)-N-methylcarbamoyl group, N-(2-trifluoro-
 methylphenyl)-N-methylcarbamoyl group, N-(4-trifluoro-
 methylphenyl)-N-methylcarbamoyl group, N-benzyl-N-
 phenylcarbamoyl group, N-benzyl-N-(2-fluorophenyl)-
 20 carbamoyl group, N-benzyl-N-(3-fluorophenyl)carbamoyl
 group, N-benzyl-N-(4-fluorophenyl)carbamoyl group, N-
 benzyl-N-(2-chlorophenyl)carbamoyl group, N-benzyl-N-
 (3-chlorophenyl)carbamoyl group, N-benzyl-N-(4-chloro-
 phenyl)carbamoyl group, N-benzyl-N-(2-bromophenyl)-
 25 carbamoyl group, N-benzyl-N-(3-bromophenyl)carbamoyl
 group, N-benzyl-N-(4-bromophenyl)carbamoyl group, N-
 benzyl-N-(2-iodophenyl)carbamoyl group, N-benzyl-N-(3-
 iodophenyl)carbamoyl group, N-benzyl-N-(4-iodophenyl)-

- carbamoyl group, N-benzyl-N-(2,3-difluorophenyl)-
 carbamoyl group, N-benzyl-N-(3,4-difluorophenyl)-
 carbamoyl group, N-benzyl-N-(3,5-difluorophenyl)-
 carbamoyl group, N-benzyl-N-(2,4-difluorophenyl)-
 5 carbamoyl group, N-benzyl-N-(2,6-difluorophenyl)-
 carbamoyl group, N-benzyl-N-(2,3-dichlorophenyl)-
 carbamoyl group, N-benzyl-N-(3,4-dichlorophenyl)-
 carbamoyl group, N-benzyl-N-(3,5-dichlorophenyl)-
 carbamoyl group, N-benzyl-N-(2,4-dichlorophenyl)-
 10 carbamoyl group, N-benzyl-N-(2,6-dichlorophenyl)-
 carbamoyl group, N-benzyl-N-(3,4,5-triifluorophenyl)-
 carbamoyl group, N-benzyl-N-(3,4,5-trichlorophenyl)-
 carbamoyl group, N-benzyl-N-(2,3-difluorophenyl)-
 carbamoyl group, N-benzyl-N-(2,4,6-trichlorophenyl)-
 15 carbamoyl group, N-benzyl-N-(2-methylphenyl)carbamoyl
 group, N-benzyl-N-(3-methylphenyl)carbamoyl group, N-
 benzyl-N-(4-methylphenyl)carbamoyl group, N-benzyl-N-
 (2-methyl-3-chlorophenyl)carbamoyl group, N-benzyl-N-
 (3-methyl-4-chlorophenyl)carbamoyl group, N-benzyl-N-
 20 (2-chloro-4-methylphenyl)carbamoyl group, N-benzyl-N-
 (2-methyl-3-fluorophenyl)carbamoyl group, N-benzyl-N-
 (2-trifluoromethylphenyl)carbamoyl group, N-benzyl-N-
 (3-trifluoromethylphenyl)carbamoyl group, N-benzyl-N-
 (4-trifluoromethylphenyl)carbamoyl group, 2-
 25 pentafluoroethylphenylcarbamoyl group, 3-
 pentafluoroethylphenylcarbamoyl group, 4-
 pentafluoroethylphenylcarbamoyl group, 2-
 isopropylphenylcarbamoyl group, 3-isopropylphenyl-

- carbamoyl group, 4-isopropylphenylcarbamoyl group, 2-tert-butylphenylcarbamoyl group, 3-tert-butylphenylcarbamoyl group, 4-tert-butylphenylcarbamoyl group, 2-sec-butylphenylcarbamoyl group, 3-sec-butylphenyl-
- 5 carbamoyl group, 4-sec-butylphenylcarbamoyl group, 2-n-heptafluoropropylphenylcarbamoyl group, 3-n-heptafluoropropylphenylcarbamoyl group, 4-n-heptafluoropropylphenylcarbamoyl group, 4-pentylphenylcarbamoyl group, 4-hexylphenylcarbamoyl group, 2-
- 10 methoxyphenylcarbamoyl group, 3-methoxyphenylcarbamoyl group, 4-methoxyphenylcarbamoyl group, 2-methoxy-3-chlorophenylcarbamoyl group, 2-fluoro-3-methoxyphenylcarbamoyl group, 2-fluoro-4-methoxyphenylcarbamoyl group, 2,6-
- 15 dimethoxyphenylcarbamoyl group, 2,3,4-trifluorophenylcarbamoyl group, 3,4,5-trifluorophenylcarbamoyl group, 2-trifluoromethoxyphenylcarbamoyl group, 3-trifluoromethoxyphenylcarbamoyl group, 4-trifluoromethoxyphenylcarbamoyl group, 2-pentafluoroethoxyphenyl-
- 20 carbamoyl group, 3-pentafluoroethoxyphenylcarbamoyl group, 4-pentafluoroethoxyphenylcarbamoyl group, 2-isopropoxyphenylcarbamoyl group, 3-isopropoxyphenylcarbamoyl group, 4-isopropoxyphenylcarbamoyl group, 2-tert-butoxyphenylcarbamoyl group, 3-tert-butoxyphenyl-
- 25 carbamoyl group, 4-tert-butoxyphenylcarbamoyl group, 2-sec-butoxyphenylcarbamoyl group, 3-sec-butoxyphenylcarbamoyl group, 4-sec-butoxyphenylcarbamoyl group, 2-n-heptafluoropropoxyphenylcarbamoyl group, 3-n-

- heptafluoropropoxyphenylcarbamoyl group, 4-n-heptafluoropropoxyphenylcarbamoyl group, 4-pentyloxyphenylcarbamoyl group, 4-hexyloxyphenylcarbamoyl group, 2-dimethylaminophenylcarbamoyl group, 2,4-dimethyl-
- 5 aminophenylcarbamoyl group, 2,4,6-trimethylamino-phenylcarbamoyl group, 3-dimethylaminophenylcarbamoyl group, 4-methylaminophenylcarbamoyl group, 2-carboxyphenylcarbamoyl group, 3-carboxyphenylcarbamoyl group, 4-carboxyphenylcarbamoyl group, 2,3-dicarboxy-
- 10 phenylcarbamoyl group, 2,4,6-tricarboxyphenylcarbamoyl group, 2-methoxycarbonylphenylcarbamoyl group, 3-methoxycarbonylphenylcarbamoyl group, 4-methoxycarbonylphenylcarbamoyl group, 2-ethoxycarbonylphenyl-
- 15 4-ethoxycarbonylphenylcarbamoyl group, 2-propoxycarbonylphenylcarbamoyl group, 3-propoxycarbonylphenylcarbamoyl group, 4-propoxycarbonylphenylcarbamoyl group, 2-(1-piperazinyl)phenylcarbamoyl group, 2-(2,4-dimethyl-1-piperazinyl)phenylcarbamoyl group, 2-(2,3,4-
- 20 trimethyl-1-piperazinyl)phenylcarbamoyl group, 2-(4-methyl-1-piperazinyl)phenylcarbamoyl group, 3-(4-methyl-1-piperazinyl)phenylcarbamoyl group, 4-(4-methyl-1-piperazinyl)phenylcarbamoyl group, 2-morpholinophenylcarbamoyl group, 3-
- 25 morpholinophenylcarbamoyl group, 4-morpholinophenylcarbamoyl group or the like.

A phenyl C1-6 alkylcarbamoyl group (which may be substituted on the phenyl ring by at least one group

selected from a group consisting of a halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group) includes a phenyl C1-6 alkylcarbamoyl group (which may be substituted on the phenyl ring by 1 to 3 groups selected from a group consisting of a halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group), for example, a benzylcarbamoyl group, 1-phenylethylcarbamoyl group, 2-phenylethylcarbamoyl group, 3-phenylpropylcarbamoyl group, 4-phenylbutylcarbamoyl group, 5-phenylpentylcarbamoyl group, 6-phenylhexylcarbamoyl group, 2-methyl-3-phenylpropylcarbamoyl group, 1,1-dimethyl-2-phenylethylcarbamoyl group, 2-methylbenzylcarbamoyl group, 3-methylbenzylcarbamoyl group, 4-methylbenzylcarbamoyl group, 2,4-dimethylbenzylcarbamoyl group, 2,4,6-trimethylbenzylcarbamoyl group, 4-trifluoromethyl-3-methoxybenzylcarbamoyl group, 2-ethylbenzylcarbamoyl group, 3-ethylbenzylcarbamoyl group, 4-ethylbenzylcarbamoyl group, 2-isopropylbenzylcarbamoyl group, 3-isopropylbenzylcarbamoyl group, 4-isopropylbenzylcarbamoyl group, 2,4-dimethoxybenzylcarbamoyl group, 2,4,6-trimethoxybenzylcarbamoyl group, 4-trifluoromethoxy-3-methylbenzylcarbamoyl group, 4-methoxybenzylcarbamoyl group, 2-ethoxybenzylcarbamoyl group, 3-ethoxybenzylcarbamoyl group, 4-ethoxybenzylcarbamoyl group, 2-isopropoxybenzylcarbamoyl group, 3-

isopropoxybenzylcarbamoyl group, 4-isopropoxybenzylcarbamoyl group, 4-trifluoromethylbenzylcarbamoyl group, 4-pentafluoroethylbenzylcarbamoyl group, 4-n-heptafluoropropylbenzylcarbamoyl group, 4-trifluoro-
5 methoxybenzylcarbamoyl group, 4-pentafluoroethoxybenzylcarbamoyl group, 4-n-heptafluoropropoxybenzylcarbamoyl group or the like.

A piperazinylcarbonyl group (which may be substituted on the piperazine ring by at least one
10 group selected from a group consisting of a C1-6 alkoxy carbonyl group, phenyl C1-6 alkoxy carbonyl group which may have at least one halogen-substituted or unsubstituted C1-6 alkyl group on the phenyl ring and phenyl C1-6 alkyl group which may have at least one
15 halogen-substituted or unsubstituted C1-6 alkyl group on the phenyl ring) includes a piperazinylcarbonyl group (which may be substituted on the piperazine ring by 1 to 3 groups selected from a group consisting of a C1-6 alkoxy carbonyl group, phenyl C1-6 alkoxy carbonyl
20 group which may have 1 to 3 halogen-substituted or unsubstituted C1-6 alkyl groups on the phenyl ring and phenyl C1-6 alkyl group which may have 1 to 3 halogen-substituted or unsubstituted C1-6 alkyl groups on the phenyl ring), for example, a 1-piperazinylcarbonyl
25 group, 2-piperazinylcarbonyl group, 3-piperazinylcarbonyl group, 4-piperazinylcarbonyl group, 4-tert-butoxycarbonyl-1-piperazinylcarbonyl group, 4-(4-methylbenzyloxycarbonyl)-1-piperazinylcarbonyl group,

4-(2,4-dimethylbenzyloxycarbonyl)-1-piperazinylcarbonyl group, 4-(2,4,6-trimethylbenzyloxycarbonyl)-1-piperazinylcarbonyl group, 4-(4-trifluoromethylbenzyloxycarbonyl)-1-piperazinylcarbonyl group, 4-(4-methylbenzyl)-1-piperazinylcarbonyl group, 4-(3,4-dimethylbenzyl)-1-piperazinylcarbonyl group, 4-(3,4,5-trimethylbenzyl)-1-piperazinylcarbonyl group, 4-(4-trifluoromethylbenzyl)-1-piperazinylcarbonyl group, 4-methoxycarbonyl-3-benzyl-1-piperazinylcarbonyl group, 4-benzyloxycarbonyl-3,5-dimethoxycarbonyl-1-piperazinylcarbonyl group or the like.

A phenyl C1-6 alkoxy group (the phenyl group may have at least one group selected from a group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group, as a substituent on the phenyl ring) is a phenyl C1-6 alkoxy group which may be substituted by 1 to 5, preferably 1 to 3 groups selected from a group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group, as defined above, examples of which include a benzyloxy group, 2-phenylethoxy group, 3-phenylpropoxy group, 2-phenylpropoxy group, 4-phenylbutoxy group, 5-phenylpentoxy group, 4-phenylpentoxy group, 6-phenylhexyloxy group, 2-fluorobenzyloxy group, 3-fluorobenzyloxy group, 4-fluorobenzyloxy group, 2-(2-fluorophenyl)ethoxy group, 2-(3-fluorophenyl)ethoxy

group, 2-(4-fluorophenyl)ethoxy group, 2-chloro-benzyloxy group, 3-chlorobenzyloxy group, 4-chlorobenzyloxy group, 2-fluoro-4-bromobenzyloxy group, 4-chloro-3-fluorobenzyloxy group, 2,3,4-trichloro-
5 benzyloxy group, 3,4,5-trifluorobenzyloxy group, 2,3,4,5,6-pentafluorobenzyloxy group, 2,4,6-trichlorobenzyloxy group, 4-isopropylbenzyloxy group, 4-n-butylbenzyloxy group, 4-methylbenzyloxy group, 2-methylbenzyloxy group, 3-methylbenzyloxy group, 2,4-
10 dimethylbenzyloxy group, 2,3-dimethylbenzyloxy group, 2,6-dimethylbenzyloxy group, 3,5-dimethylbenzyloxy group, 2,5-dimethylbenzyloxy group, 2,4,6-trimethylbenzyloxy group, 3,5-di(trifluoromethyl)benzyloxy group, 4-isopropoxybenzyloxy group, 4-n-butoxybenzyloxy
15 group, 4-methoxybenzyloxy group, 2-methoxybenzyloxy group, 3-methoxybenzyloxy group, 2,4-dimethoxybenzyloxy group, 2,3-dimethoxybenzyloxy group, 2,6-dimethoxybenzyloxy group, 3,5-dimethoxybenzyloxy group, 2,5-dimethoxybenzyloxy group, 2,4,6-trimethoxybenzyloxy
20 group, 3,5-di(trifluoromethoxy)benzyloxy group, 2-isopropoxybenzloxy group, 3-chloro-4-methoxybenzyloxy group, 2-chloro-4-trifluoromethoxybenzyloxy group, 3-methyl-4-fluorobenzyloxy group, 4-bromo-3-trifluoromethylbenzyloxy group, 2-(2-chlorophenyl)-
25 ethoxy group, 2-(3-chlorophenyl)ethoxy group, 2-(4-chlorophenyl)ethoxy group, 2-trifluoromethylbenzyloxy group, 3-trifluoromethylbenzyloxy group, 4-trifluoromethylbenzyloxy group, 2-trifluoromethoxybenzyloxy

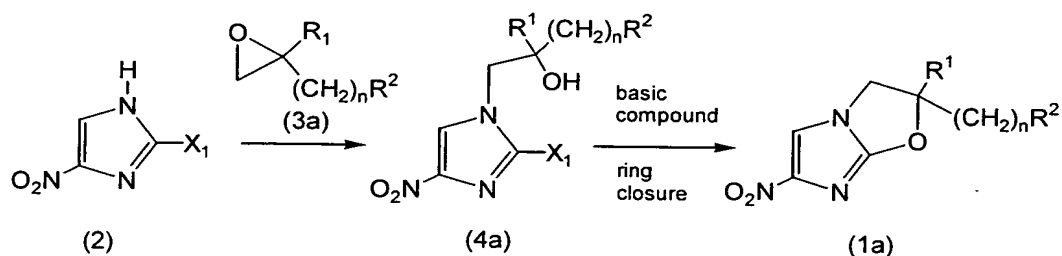
group, 3-trifluoromethoxybenzyloxy group, 4-trifluoromethoxybenzyloxy group, 2-(2-trifluoromethylphenyl)ethoxy group, 2-(3-trifluoromethylphenyl)ethoxy group, 2-(4-trifluoromethylphenyl)ethoxy group, 2-(2-trifluoromethoxyphenyl)ethoxy group, 2-(3-trifluoromethoxyphenyl)ethoxy group, 2-(4-trifluoromethoxyphenyl)ethoxy group, 3-(2-trifluoromethylphenyl)propoxy group, 3-(3-trifluoromethylphenyl)propoxy group, 3-(4-trifluoromethylphenyl)propoxy group, 3-(2-trifluoromethylphenyl)propoxy group, 3-(3-trifluoromethoxyphenyl)propoxy group, 3-(4-trifluoromethoxyphenyl)propoxy group, 4-(3-trifluoromethylphenyl)butoxy group, 5-(4-trifluoromethylphenyl)pentoxy group, 4-(4-trifluoromethylphenyl)pentoxy group, 4-(4-trifluoromethoxyphenyl)pentoxy group, 6-(3-trifluoromethylphenyl)hexyloxy group, 6-(4-trifluoromethylphenyl)hexyloxy group, 6-(4-trifluoromethoxyphenyl)hexyloxy group, or the like.

A C3-8 cycloalkyl-C1-6 alkyl group is a group consisting of a cyclic alkyl group having 3 to 8 carbon atoms and an alkyl group having 1 to 6 carbon atoms, examples of which include a cyclopropylmethyl group, 2-cyclopropylethyl group, 3-cyclopropylpropyl group, 4-cyclopropylbutyl group, 5-cyclopropylpentyl group, 6-cyclopropylhexyl group, cyclobutylmethyl group, 2-cyclobutylethyl group, 3-cyclobutylpropyl group, 4-cyclobutylbutyl group, 5-cyclobutylpentyl group, 6-cyclobutylhexyl group, cyclopentylmethyl group, 2-

cyclopentylethyl group, 3-cyclopentylpropyl group, 4-cyclopentylbutyl group, 5-cyclopentylpentyl group, 6-cyclopentylhexyl group, cyclohexylmethyl group, 2-cyclohexylethyl group, 3-cyclohexylpropyl group, 4-cyclohexylbutyl group, 5-cyclohexylpentyl group, 6-cyclohexylhexyl group, cycloheptylmethyl group, 2-cycloheptylethyl group, 3-cycloheptylpropyl group, 4-cycloheptylbutyl group, 5-cycloheptylpentyl group, 6-cycloheptylhexyl group, cyclooctylmethyl group, 2-cyclooctylethyl group, 3-cyclooctylpropyl group, 4-cyclooctylbutyl group, 5-cyclooctylpentyl group, 6-cyclooctylhexyl group or the like.

The methods for producing the compounds of the present invention are explained below.

15 Reaction scheme 1



wherein R^1 , R^2 and n are the same as above, and X_1 represents a halogen atom or nitro group.

According to reaction scheme 1, the compound of the present invention represented by general formula (1a) is produced by reacting a 4-nitroimidazole

compound represented by general formula (2) with an epoxy compound represented by general formula (3a) in the presence or absence of a basic compound to obtain a compound represented by general formula (4a), and then
5 subjecting the obtained compound to a ring closure reaction.

The molar ratio of the compound of general formula (2) to the compound of general formula (3a) may be generally between 1 : 0.5 and 1 : 5, and preferably
10 between 1 : 0.5 and 1 : 3.

Known compounds can be widely used as a basic compound herein. Examples of such a basic compound include inorganic basic compounds such as a metal hydride, metal alcoholate, hydroxide, carbonate or
15 hydrogencarbonate, and organic basic compounds such as acetate.

Specific examples of a metal hydride include sodium hydride and potassium hydride. Specific examples of a metal alcoholate include sodium
20 methoxide, sodium ethoxide and potassium tert-butoxide. Specific examples of a hydroxide include sodium hydroxide and potassium hydroxide. Specific examples of a carbonate include sodium carbonate and potassium carbonate. Specific examples of a hydrogencarbonate
25 include sodium hydrogencarbonate and potassium hydrogencarbonate. In addition to the above compounds, sodium amide and the like may also be included in the inorganic basic compounds.

Specific examples of acetate include sodium acetate and potassium acetate. In addition to these compounds, specific examples of organic basic compounds include triethylamine, trimethylamine, diisopropyl-
5 ethylamine, pyridine, dimethylaniline, 1-methyl-pyrrolidine, N-methylmorpholine, 1,5-diazabicyclo-[4.3.0]nonene-5(DBN), 1,8-diazabicyclo[5.4.0]undecene-7(DBU), and 1,4-diazabicyclo[2.2.2]octane(DABCO).

The molar ratio of the above basic compound
10 to the compound of general formula (2) may be generally between 0.1 : 1 and 2 : 1, preferably between 0.1 : 1 and 1 : 1, and more preferably between 0.1 : 1 and 0.5 : 1.

The reaction of the compound of general
15 formula (2) with the compound of general formula (3a) is generally carried out in an appropriate solvent.

Common solvents can be widely used as the above solvent, as long as it does not inhibit the reaction. Examples of such a solvent include aprotic
20 polar solvents such as dimethylformamide (DMF), dimethylsulfoxide (DMSO) or acetonitrile, ketone solvents such as acetone or methylethylketone, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, alcohol solvents such as
25 methanol, ethanol, isopropanol, n-butanol or tert-butanol, ether solvents such as tetrahydrofuran (THF), dioxane, dipropyl ether, diethyl ether or diglyme, ester solvents such as ethyl acetate or methyl acetate,

and mixed solvents thereof. Water may be contained in these solvents.

The reaction of the compound of general formula (2) with the compound of general formula (3a) is carried out, for example, as follows: The compound of general formula (2) is dissolved in a reaction solvent, and while stirring, a basic compound is added to the mixture cooled on ice or at up to room temperature (30°C). Thereafter, the mixture is stirred at room temperature to 80°C for 30 minutes to 1 hour, and the compound of general formula (3a) is then added thereto. Thereafter, the mixture is further stirred generally at room temperature to 100°C, and preferably 50°C to 80°C, generally for 30 minutes to 60 hours, and preferably for 1 to 50 hours.

The compound (2) used as a starting material is known. The compound (3a) includes a novel compound, and a method for producing the compound will be explained later.

The thus obtained reaction mixture is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, a compound of general formula (4a) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

The compound of the present invention

represented by general formula (1a) is produced by
subjecting the compound represented by general formula
(4a) to a ring closure reaction. The ring closure
reaction is carried out by dissolving the above
5 obtained compound represented by general formula (4a)
in a reaction solvent and then adding a basic compound
thereto followed by stirring.

Herein, as a reaction solvent and a basic
compound, there can be used the same reaction solvent
10 and the same basic compound as used in the above
reaction of the compound of general formula (2) with
the compound of general formula (3a).

The molar ratio of the basic compound to the
compound of general formula (4a) is generally equal to
15 1 : 1 or higher, preferably between 1 : 1 and 5 : 1,
and more preferably between 1 : 1 and 2 : 1.

The reaction temperature for the ring closure
reaction is generally 0°C to 150°C, preferably room
temperature to 120°C, and more preferably 50°C to 100°C.
20 The reaction time is generally 30 minutes to 48 hours,
preferably 1 to 24 hours, and more preferably 1 to 12
hours.

The thus obtained reaction mixture is, for
example, cooled, and then its crude reaction product is
25 separated therefrom by an isolation operation such as
filtration, concentration or extraction. Thereafter,
the compound of general formula (1a) can be isolated
and purified from the reaction mixture by a common

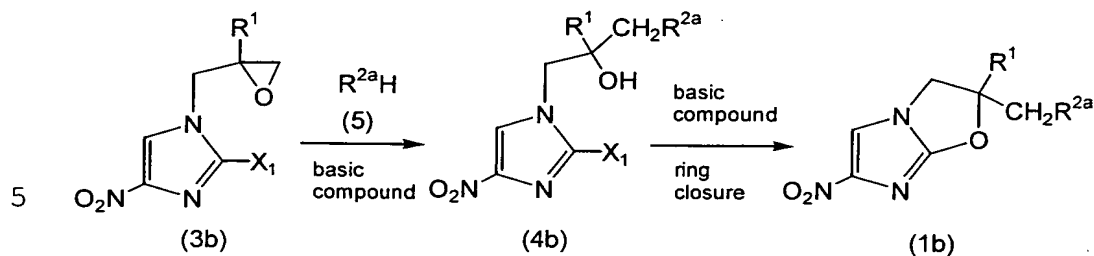
purification operation such as column chromatography or recrystallization.

In the present invention, the reaction mixture can be directly subjected to the following ring closure reaction without isolating the compound of general formula (4a) generated as a result of the reaction of the compound of general formula (2) with the compound of general formula (3a). For example, the compound of general formula (2) is reacted with the compound of general formula (3a) at room temperature to 80°C, and thereafter, a basic compound is added to the obtained reaction mixture followed by stirring at 50°C to 100°C. Otherwise, after the compound of general formula (2) is reacted with the compound of general formula (3a) at room temperature to 80°C, the obtained reaction mixture is concentrated, and the residue is dissolved in a high boiling solvent. Thereafter, a basic compound is added to the obtained solution followed by stirring at 50°C to 100°C, so as to produce a compound of interest represented by general formula (1a).

Alternatively, in the reaction of the compound of general formula (2) with the compound of general formula (3a), a basic compound is used at a molar ratio of the basic compound to the compound (2) that is between 0.9 : 1 and 2 : 1. The stirring is carried out at 50°C to 100°C, so that the reaction of the compound of general formula (2) with the compound

of general formula (3a) is carried out in a single process to produce a compound of interest represented by general formula (1a).

Reaction scheme 2



wherein R^1 and X_1 are the same as above, and R^{2a} represents a group represented by general formula (A), (B), (E) or (F).

According to reaction scheme 2, the compound
 10 of the present invention represented by general formula (1b) is produced by reacting a compound represented by general formula (3b) with a compound represented by general formula (5) or a salt thereof, so as to obtain a compound represented by general formula (4b), and
 15 then subjecting the obtained compound to a ring closure reaction, in the presence of a basic compound.

The compound (3b) is novel, and a method for producing the compound will be explained later (reaction scheme 13). The compound (5), in which R^{2a}
 20 represents a group represented by general formula (E), includes a novel compound. An example of methods for producing the above compound will be described later in

Reference Examples 182, 186 to 188, and 192.

The molar ratio of the compound of general formula (3b) to the compound of general formula (5) may be generally between 1 : 0.5 and 1 : 5, and preferably
5 between 1 : 0.5 and 1 : 2.

The reaction of the compound of general formula (3b) with the compound of general formula (5) is carried out in the presence of a basic compound in an appropriate solvent.

10 As a basic compound and a reaction solvent, there can be used the same basic compound and the same reaction solvent as used in the above reaction of the compound of general formula (2) with the compound of general formula (3a). The molar ratio of the basic
15 compound to the compound of general formula (3b) is generally a catalytic amount, preferably between 0.1 : 1 and 3 : 1, and more preferably between 0.1 : 1 and 2 : 1.

In the case of the compound (5) in which R^{2a}
20 represents a group represented by general formula (B) or (E), the salt of the compound (5) can be used instead of using the compound (5) and a basic compound. Examples of such a salt include alkali metal salts such as a sodium salt or a potassium salt of the compound
25 (5).

The reaction of the compound of general formula (3b) with the compound of general formula (5) is carried out, generally at room temperature to 150°C,

preferably at room temperature to 120°C, and more preferably at room temperature to 80°C. The reaction time is generally 10 minutes to 48 hours, preferably 10 minutes to 24 hours, and more preferably 10 minutes to 5 2 hours.

The thus obtained reaction mixture is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, 10 the compound of general formula (4b) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

The compound of the present invention 15 represented by general formula (1b) is produced by subjecting the compound represented by general formula (4b) to a ring closure reaction. The ring closure reaction is carried out by dissolving the above obtained compound represented by general formula (4b) 20 in a reaction solvent and then adding a basic compound thereto followed by stirring at a certain temperature.

Herein, as a reaction solvent and a basic compound, there can be used the same reaction solvent and the same basic compound as used in the above 25 reaction of the compound of general formula (3b) with the compound of general formula (5).

The molar ratio of the basic compound to the compound of general formula (4b) is generally equal to

1 : 1 or higher, preferably between 1 : 1 and 5 : 1, and more preferably between 1 : 1 and 2 : 1.

The reaction temperature for the ring closure reaction is generally 0°C to 150°C, preferably room temperature to 120°C, and more preferably 50°C to 100°C. The reaction time is generally 10 minutes to 48 hours, preferably 10 minutes to 24 hours, and more preferably 20 minutes to 4 hours.

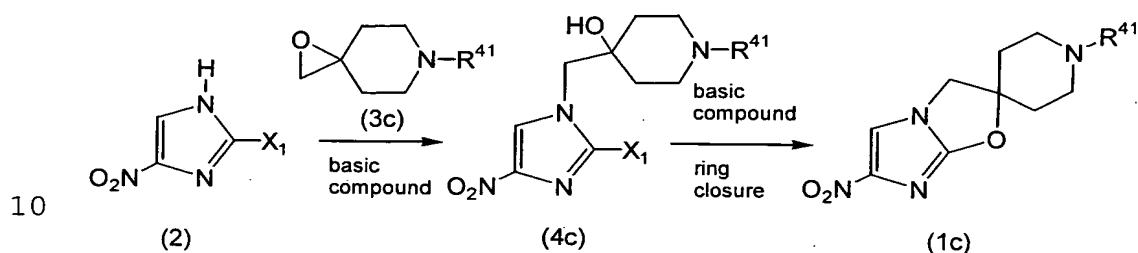
The thus obtained reaction mixture is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, the compound of general formula (1b) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

In the present invention, the reaction mixture can be directly subjected to the following ring closure reaction without isolating the compound of general formula (4b) produced as a result of the reaction of the compound of general formula (3b) with the compound of general formula (5), so as to produce a compound of interest that is the compound of the present invention represented by general formula (1b).

Particularly, in the case of the compound (5) in which R^{2a} represents a group represented by general formula (B) or (E), if a basic compound is used to the compound (5) at a molar ratio of equal to 1 : 1 or

higher, and if the reaction is carried out at 50°C to 100°C, the compound of the present invention represented by general formula (1b) can be produced in a single process without isolating an intermediate (4). In the case of using the alkali metal salt (e.g., a sodium salt or a potassium salt) of the compound (5) in which R^{2a} represents a group represented by general formula (B) or (E), the same thing can be said.

Reaction scheme 3



wherein R^{41} and X_1 are the same as above.

According to reaction scheme 3, the compound of the present invention represented by general formula (1c) is produced by reacting the compound represented by general formula (2) with a compound represented by general formula (3c) so as to obtain a compound represented by general formula (4c), and then subjecting the obtained compound to a ring closure reaction, in the presence of a basic compound.

20 The compound (3c) includes a novel compound, and a method for producing the compound will be explained later (reaction scheme 14).

The molar ratio of the compound of general formula (2) to the compound of general formula (3c) may be generally between 0.1 : 1 and 2 : 1, preferably between 0.1 : 1 and 1 : 1, and more preferably between
5 0.1 : 1 and 0.5 : 1.

The reaction of the compound of general formula (2) with the compound of general formula (3c) is carried out in the presence of a basic compound in an appropriate solvent.

10 As a basic compound and a reaction solvent, there can be used the same basic compound and the same reaction solvent as used in the above reaction of the compound of general formula (2) with the compound of general formula (3a). The molar ratio of the basic
15 compound to the compound of general formula (2) is generally 0.1 : 1 or higher, preferably between 1 : 1 and 5 : 1, and more preferably between 1 : 1 and 2 : 1.

The reaction of the compound of general formula (2) with the compound of general formula (3c)
20 is carried out, for example, as follows: The compound of general formula (2) is dissolved in a reaction solvent, and while stirring, a basic compound is added to the mixture cooled on ice or at up to room temperature (30°C). Thereafter, the mixture is stirred at room
25 temperature to 80°C for 30 minutes to 1 hour, and the compound of general formula (3c) is then added thereto. Thereafter, the mixture is further stirred generally at room temperature to 100°C, and preferably 50°C to 80°C,

generally for 30 minutes to 24 hours, preferably for 1 to 12 hours, and more preferably for 1 to 8 hours.

The thus obtained reaction mixture is, for example, cooled, and then its crude reaction product is
5 separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, the compound of general formula (4c) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or
10 recrystallization.

The compound of the present invention represented by general formula (1c) is produced by subjecting the compound represented by general formula (4c) to a ring closure reaction. The ring closure
15 reaction is carried out by dissolving the above obtained compound represented by general formula (4c) in a reaction solvent and then adding a basic compound thereto followed by stirring at a certain temperature.

Herein, as a reaction solvent and a basic
20 compound, there can be used the same reaction solvent and the same basic compound as used in the above reaction of the compound of general formula (2) with the compound of general formula (3c).

The molar ratio of the basic compound to the
25 compound of general formula (4c) is generally equal to 1 : 1 or higher, preferably between 1 : 1 and 5 : 1, and more preferably between 1 : 1 and 2 : 1.

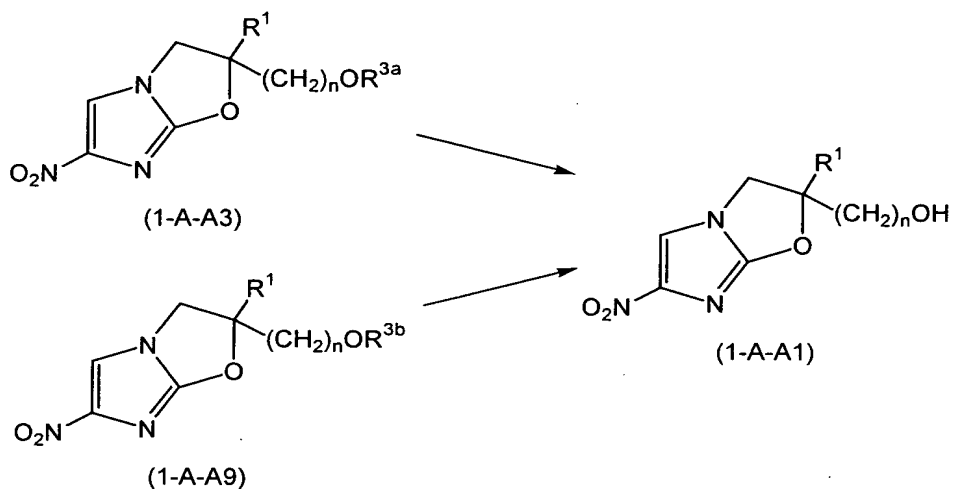
The reaction temperature for the ring closure

reaction is generally 0°C to 150°C, preferably room temperature to 120°C, and more preferably 50°C to 100°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours, and more preferably 1 to 12
5 hours.

The thus obtained reaction mixture is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter,
10 the compound of general formula (1c) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

In the present invention, the reaction
15 mixture can be directly subjected to the following ring closure reaction without isolating the compound of general formula (4c) generated as a result of the reaction of the compound of general formula (2) with the compound of general formula (3c), so that the
20 compound of interest of the present invention represented by general formula (1c) can be produced.

Reaction scheme 4



wherein R^1 and n are the same as above, R^{3a} represents a C1-C6 alkoxy-C1-C6 alkyl group, and R^{3b} represents a C1-C6 alkanoyl group.

5 A compound wherein, in general formula (1), R^2 represents a group represented by general formula (A) and R^3 represents A1) a hydrogen atom (hereinafter referred to as a compound (1-A-A1)), is produced by the hydrolysis of a corresponding compound in which R^3 represents A3) a C1-C6 alkoxy-C1-C6 alkyl group (hereinafter referred to as a compound (1-A-A3)), or a corresponding compound wherein R^3 represents A9) a C1-C6 alkanoyl group (hereinafter referred to as a compound (1-A-A9)).

15 Hydrolysis of the compound (1-A-A3) is carried out under acidic conditions. The hydrolysis is carried out, for example, by suspending or dissolving the compound (1-A-A3) in an appropriate solvent, and

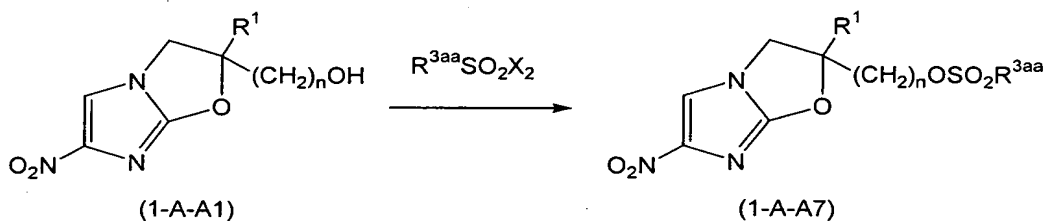
adding acid to the obtained solution followed by stirring at 0°C to 120°C. Example of the used solvent may include water, alcohol solvents such as methanol, ethanol, isopropanol or ethylene glycol, acetonitrile, acetone, toluene, DMF, DMSO, acetic acid, trifluoroacetic acid, and mixed solvents thereof. Examples of the used acid may include organic acids such as trifluoroacetic acid or acetic acid, and inorganic acids such as hydrochloric acid, bromic acid, hydrobromic acid or sulfuric acid. Organic acids such as trifluoroacetic acid or acetic acid can also be used as reaction solvents. The reaction temperature is generally 0°C to 120°C, preferably room temperature to 100°C, and more preferably room temperature to 80°C. The reaction time is generally 30 minutes to 24 hours, preferably 30 minutes to 12 hours, and more preferably 1 to 8 hours.

Hydrolysis of the compound (1-A-A9) is carried out under basic condition. The hydrolysis is carried out, for example, by suspending or dissolving the compound (1-A-A9) in an appropriate solvent, and adding base to the obtained solution followed by stirring at 0°C to 120°C. Example of the used solvent may include water, alcohol solvents such as methanol, ethanol, isopropanol or ethylene glycol, and mixed solvents thereof. Examples of the used base may include alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkali metal

carbonates such as sodium carbonate or potassium carbonate, and acetates such as sodium acetate. The reaction temperature is generally 0°C to 120°C, preferably room temperature to 100°C, and more preferably room temperature to 80°C. The reaction time is generally 30 minutes to 24 hours, preferably 30 minutes to 12 hours, and more preferably 1 to 8 hours.

The thus obtained reaction mixture is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, the compound (1-A-A1) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

Reaction scheme 5



wherein R¹ and n are the same as above, X₂ represents a halogen atom, and R^{3aa} represents a C1-C6 alkyl group or phenyl group which may be substituted by the C1-C6 alkyl group.

A compound wherein, in general formula (1), R² represents a group represented by general formula (A)

and R^3 represents a sulfonyl group of the definitions A7) or A8) (hereinafter referred to as a compound (1-A-A7)), is produced by the sulfonylation of a corresponding compound wherein R^3 represents A1) a
5 hydrogen atom (the compound (1-A-A1)).

For the sulfonylation of the compound (1-A-A1), reaction conditions for the common sulfonylation reaction of alcohol can be widely applied. For example, the compound (1-A-A1) is dissolved in an
10 appropriate solvent, and the compound represented by general formula $R^{3aa}SO_2X_2$ is added to the obtained solution in the presence of a basic compound followed by stirring at 0°C to 150°C, so that the compound (1-A-A7) can be obtained.

15 Any solvent can be used herein, as long as it does not inhibit the sulfonylation reaction. Examples of such a solvent include halogenated hydrocarbon solvents such as methylene chloride or chloroform, aprotic polar solvents such as DMF, DMSO or
20 acetonitrile, aromatic hydrocarbon solvents such as benzene, toluene or xylene, hydrocarbon solvents such as tetralin, liquid paraffin or cyclohexane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, ethyl acetate, acetone, and mixed
25 solvents thereof.

The compound represented by general formula $R^{3aa}SO_2X_2$ is used to the compound (1-A-A1) at a molar ratio of generally equal to 1 : 1 or higher, preferably

between 1 : 1 and 2 : 1, and more preferably between 1 : 1 and 1.1 : 1.

As a basic compound, there can be used the same basic compound as used in the above reaction of the compound of general formula (2) with the compound of general formula (3a).

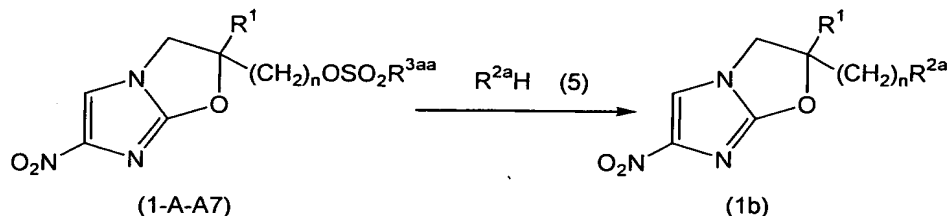
The molar ratio of the basic compound to the compound represented by general formula $R^{3aa}SO_2X_2$ is generally equal to 1 : 1 or higher, preferably between 1 : 1 and 5 : 1, and more preferably between 1 : 1 and 2 : 1.

In the present sulfonylation reaction, 4-dimethylaminopyridine, 4-(1-pyrrolidinyl)pyridine or the like can be used as a catalyst.

The reaction temperature is generally 0°C to 150°C, preferably 0°C to 100°C, and more preferably 0°C to 60°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours, and more preferably 1 to 4 hours.

The thus obtained reaction mixture is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, the compound (1-A-A7) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

Reaction scheme 6



wherein R^1 , $\text{R}^{2\text{a}}$, $\text{R}^{3\text{aa}}$ and n are the same as above.

A compound wherein, in general formula (1), R^2 represents a group represented by general formula (A), (B), (E) or (F) (hereinafter referred to as a compound (1b)), is also produced by the reaction of a corresponding compound wherein R^2 represents a group represented by general formula (A) and R^3 represents a sulfonyl group of the definitions A7) or A8) (a compound (1-A-A7)) with a compound represented by general formula (5).

The reaction of the compound (1-A-A7) with the compound represented by general formula (5) is carried out in an appropriate solvent in the presence of a basic compound.

Any solvent can be used herein, as long as it does not inhibit the present reaction. Examples of such a solvent include water, aprotic polar solvents such as DMF, DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin, liquid paraffin or cyclohexane, alcohol solvents such as

ethanol, isopropanol, n-butanol or tert-butanol, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, ethyl acetate, acetone, and mixed solvents thereof.

5 As a basic compound, there can be used the same basic compound as used in the above reaction of the compound of general formula (2) with the compound of general formula (3a).

 The molar ratio of the basic compound to the
10 compound (1-A-A7) is generally equal to 1 : 1 or higher, preferably between 1 : 1 and 5 : 1, and more preferably between 1 : 1 and 2 : 1.

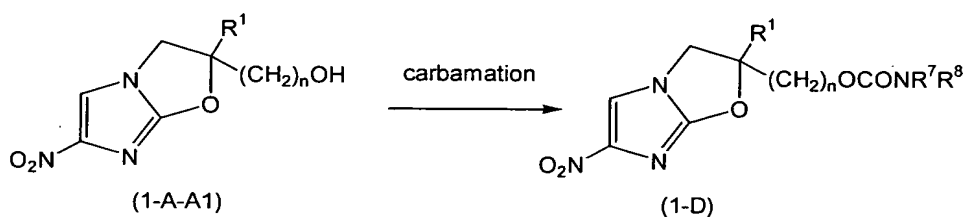
 The molar ratio of the compound represented by general formula (5) to the compound (1-A-A7) may be
15 generally equal to 1 : 1 or higher, preferably between 0.9 : 1 and 2 : 1, and more preferably between 0.9 : 1 and 1.5 : 1.

 The reaction temperature is generally room temperature to 150°C, preferably room temperature to
20 100°C, and more preferably 60°C to 100°C. The reaction time is generally 10 minutes to 24 hours, preferably 10 minutes to 12 hours, and more preferably 20 minutes to 7 hours.

 The thus obtained reaction mixture is, for
25 example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, a compound of interest can be isolated and purified from

the reaction mixture by a common purification operation such as column chromatography or recrystallization.

Reaction scheme 7



5 wherein R¹, n, R⁷ and R⁸ are the same as above.

A compound wherein, in general formula (1), R² represents a group represented by general formula (D) (hereinafter referred to as a compound (1-D)), is produced by the carbamation of a compound wherein R² represents a group represented by general formula (A) and R³ represents A1) a hydrogen atom (the compound (1-A-A1)).

For the carbamation of the compound (1-A-A1), reaction conditions for the common carbamation reaction of alcohol can be widely applied. Examples of such a method include: (1) a method using amine represented by a general formula R⁷R⁸NH (wherein R⁷ and R⁸ are the same as above) and triphosgene, (2) a reaction of using amine represented by a general formula R⁷R⁸NH (wherein R⁷ and R⁸ are the same as above) and carbodiimidazole, and (3) a method using an isocyanate compound.

(1) Method using amine and triphosgene

Amine represented by the general formula R^7R^8NH (wherein R^7 and R^8 are the same as above) is reacted with triphosgene, so as to generate carbamoyl chloride represented by a general formula $ClCONR^7R^8$ (wherein R^7 and R^8 are the same as above). Carbamoyl chloride may be isolated. However, since it is generally unstable, it is immediately used in the following step without isolation.

A basic compound and the above amine are added to a methylene chloride solution containing triphosgene, while the solution is cooled and stirred. Thereafter, the mixture is stirred at $0^{\circ}C$ to $30^{\circ}C$ for 30 minutes to 4 hours, so as to generate carbamoyl chloride. The molar ratio of triphosgene to amine is generally between 0.3 : 1 and 1.5 : 1, preferably between 0.3 : 1 and 0.6 : 1, and more preferably between 0.3 : 1 and 0.4 : 1.

Examples of a basic compound used in the reaction between amine and triphosgene include triethylamine, N-ethyldiisopropylamine, and N-methylmorpholine. The molar ratio of a basic compound to triphosgene is generally 3 : 1 or higher, preferably between 3 : 1 and 4.5 : 1, and more preferably between 3 : 1 and 3.3 : 1.

The reaction temperature is generally $0^{\circ}C$ to $60^{\circ}C$, and preferably $0^{\circ}C$ to room temperature ($30^{\circ}C$). The reaction time is generally 30 minutes to 8 hours, preferably 1 to 4 hours, and more preferably 1 to 2

hours.

The thus obtained reaction solution of carbamoyl chloride can be directly used. However, it is more advantageous to eliminate insoluble products by
5 filtration prior to concentration of the filtrate.

Subsequently, the compound (1-A-A1) is dissolved in an appropriate reaction solvent, and the carbamoyl chloride produced above is added thereto, while stirring on ice cooling. Thereafter, copper
10 chloride is further added thereto, and the mixture is stirred at a certain temperature for a certain time, so as to produce the compound (1-D).

Any reaction solvent can be widely used herein, as long as it does not inhibit the reaction.
15 Examples of such a solvent may include aprotic polar solvents such as DMF, DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane,
20 ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

The molar ratio of carbamoyl chloride to the compound (1-A-A1) may be generally between 1 : 1 and
25 5 : 1, preferably between 1 : 1 and 3 : 1, and more preferably between 1 : 1 and 2 : 1.

Moreover, the molar ratio of copper chloride to the compound (1-A-A1) may be generally between 0.1 :

1 and 5 : 1, preferably between 0.5 : 1 and 2 : 1, and more preferably between 0.5 : 1 and 1 : 1.

The reaction temperature is generally 0°C to 60°C, preferably 10°C to 50°C, and more preferably 20°C to 35°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 30 hours, and more preferably 2 to 24 hours.

(2) Reaction of using amine and carbodiimidazole

Amine represented by the general formula R^7R^8NH (wherein R^7 and R^8 are the same as above) is dissolved in an appropriate reaction solvent. 1,1'-carbonyldiimidazole is added to the obtained solution, while stirring on ice. The obtained mixture is stirred at a certain temperature for a certain time, so as to obtain an amino carbonylimidazole derivative.

The molar ratio of 1,1'-carbonyldiimidazole to amine is generally between 0.9 : 1 and 2 : 1, preferably between 1 : 1 and 1.5 : 1, and more preferably between 1 : 1 and 1.2 : 1.

Examples of the used solvent may include aprotic polar solvents such as acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

The reaction temperature is generally 0°C to

60°C, and preferably 0°C to room temperature (30°C). The reaction time is generally 30 minutes to 8 hours, preferably 1 to 4 hours, and more preferably 1 to 2 hours.

5 The compound (1-A-A1) is dissolved in an appropriate solvent in advance. Then, the above obtained amino carbonylimidazole derivative is added to the solution, while stirring on ice. Thereafter, copper chloride is further added thereto, and the
10 mixture is stirred at a certain temperature for a certain time, so as to produce the compound (1-D).

Any solvent can be widely used herein as a reaction solvent, as long as it does not inhibit the reaction. Examples of such a solvent may include
15 aprotic polar solvents such as DMF, DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents
20 such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

The molar ratio of the amino carbonyl-imidazole derivative to the compound (1-A-A1) may be
25 generally between 1 : 1 and 5 : 1, preferably between 1 : 1 and 3 : 1, and more preferably between 1 : 1 and 2 : 1.

Moreover, the molar ratio of the copper

chloride to the compound (1-A-A1) may be generally between 0.9 : 1 and 5 : 1, preferably between 1 : 1 and 2 : 1, and more preferably between 1 : 1 and 1.2 : 1.

The reaction temperature is generally 0°C to 60°C, preferably 10°C to 50°C, and more preferably 20°C to 35°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 30 hours, and more preferably 1 to 3 hours.

(3) Method using isocyanate

The compound (1-A-A1) is dissolved in an appropriate reaction solvent. Then, isocyanate is added to the solution, while stirring on ice. Thereafter, copper chloride is further added thereto, and the mixture is stirred at a certain temperature for a certain time, so as to produce a compound (1-D) in which R⁷ or R⁸ represents a hydrogen atom.

Any solvent can be widely used herein as a reaction solvent, as long as it does not inhibit the reaction. Examples of such a solvent may include aprotic polar solvents such as DMF, DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

The molar ratio of the isocyanates to the

compound (1-A-A1) may be generally between 1 : 1 and 5 : 1, preferably between 1 : 1 and 3 : 1, and more preferably between 1 : 1 and 2 : 1.

Moreover, the molar ratio of the copper chloride to the compound (1-A-A1) may be generally between 0.9 : 1 and 5 : 1, preferably between 1 : 1 and 2 : 1, and more preferably between 1 : 1 and 1.2 : 1.

The reaction temperature is generally 0°C to 60°C, preferably 10°C to 50°C, and more preferably 20°C to 35°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 30 hours, and more preferably 1 to 3 hours.

The reaction mixture obtained by the above method (1), (2) or (3) is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, the compound (1-D) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

A compound having a heterocycle containing a nitrogen atom in a molecule thereof and comprising a C1-C6 alkoxycarbonyl group substituted on the nitrogen atom of the above heterocycle selected from among the compounds of the present invention represented by general formula (1) can be converted by deprotection into a compound having a hydrogen atom that is substituted on the nitrogen atom of the corresponding

heterocycle.

According to this method, for example, a starting material to be deprotected is dissolved in an appropriate reaction solvent followed by hydrolysis
5 using acid, so as to obtain a compound of interest.

Any solvent can be widely used herein as a reaction solvent, as long as it does not inhibit the reaction. Examples of such a solvent may include water, alcohol solvents such as methanol or ethanol,
10 aprotic polar solvents such as DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane,
15 dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

Examples of acid include inorganic acids such as hydrochloric acid, bromic acid or hydrobromic acid, and organic acids such as acetic acid, trifluoroacetic
20 acid or trichloroacetic acid. Of these, the use of trifluoroacetic acid is advantageous.

The molar ratio of such acid to the starting material is generally equal to 1 : 1 or higher, and preferably between 2 : 1 and 10 : 1. However, such
25 acid may also be used a large excess amount as a reaction solvent. The reaction temperature is generally room temperature to 100°C, but it may be appropriately adjusted depending on the type of the used acid. When

trifluoroacetic acid is used, it is enough to set at room temperature. The reaction time is generally 1 to 24 hours, and preferably 1 to 12 hours.

The thus obtained reaction mixture is concentrated, and if necessary, acid such as hydrochloric acid is added thereto for crystallization, so that a compound of interest can be isolated in a form of hydrochloride or trifluoroacetate by recrystallization or the like.

The deprotected compound of interest can be isolated as described above. Alternatively, a basic compound such as triethylamine is added thereto without isolation, so that the compound of interest is converted into a free compound, which can be used in the following reaction.

For example, the above free base compound of interest is reacted with an acid halide, acid anhydride or mixed acid anhydride, so that the corresponding amide or carbamate can be produced. The reaction of the above free base compound of interest with sulfonyl chloride enables the production of the corresponding sulfon amide. Moreover, the ureation of the above free base compound of interest with amine enables the production of the corresponding urea. Furthermore, the reductive amination of the above free base compound of interest with aldehyde or the alkylation of the same above compound with alkyl halide enables the production of the N-alkylated derivative of the above compound of

interest.

A compound having a heterocycle containing a nitrogen atom in a molecule thereof and comprising a hydrogen atom substituted on the nitrogen atom of the
5 above heterocycle selected from among the compounds of the present invention represented by general formula (1) can be converted by carbamation into a compound having -COOR^{27} (wherein R^{27} is the same as above) substituted on the nitrogen atom of the corresponding
10 heterocycle.

Examples of a method for carbamation include (1) a method using various types of halogenated formates and (2) a method using an active intermediate obtained by reacting alcohol with carbonyldiimidazole.

15 (1) Method using halogenated formate

A starting material is reacted with halogenated formate in a reaction solvent in the presence of a basic compound, so as to produce a compound of interest.

20 Any solvent can be widely used herein as a reaction solvent, as long as it does not inhibit the reaction. Examples of such a solvent may include aprotic polar solvents such as DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene,
25 tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone,

ethyl acetate, and mixed solvents thereof.

Known compounds can be widely used as a basic compound herein. Examples of such a basic compound include inorganic basic compounds such as hydroxide, carbonate or hydrogencarbonate, and organic basic compounds such as acetate.

Specific examples of hydroxide include sodium hydroxide, potassium hydroxide, cesium hydroxide and lithium hydroxide. Specific examples of carbonate include sodium carbonate, potassium carbonate, cesium carbonate and lithium carbonate. Specific examples of hydrogencarbonate include sodium hydrogencarbonate, potassium hydrogencarbonate, cesium hydrogencarbonate and lithium hydrogencarbonate.

Specific examples of acetate include sodium acetate and potassium acetate. In addition to these compounds, specific examples of other organic basic compounds include triethylamine, trimethylamine, diisopropylethylamine, pyridine, dimethylaniline, 1-methylpyrrolidine, N-methylmorpholine, DBN, DBU, and DABCO.

The molar ratio of such a basic compound to the starting material may be generally between 1 : 1 and 4 : 1, preferably between 1 : 1 and 1.5 : 1, and more preferably between 1 : 1 and 1.1 : 1.

The molar ratio of such halogenated formate to the starting material may be generally equal to 1 : 1 or higher, preferably between 1 : 1 and 1.5 : 1, and

more preferably between 1 : 1 and 1.1 : 1.

The reaction temperature is generally 0°C to 100°C, preferably 0°C to 60°C, and more preferably 10°C to 30°C. The reaction time is generally 30 minutes to 12 hours, preferably 1 to 6 hours, and more preferably 1 to 2 hours.

(2) Method using active intermediate

Alcohol represented by a general formula $R^{27}OH$ (R^{27} is the same as above) is reacted with 1,1'-carbonyldiimidazole in an appropriate solvent to obtain an active intermediate (the first step), and then the obtained active intermediate is reacted with a starting material (the second step), so that a compound of interest can be produced.

Any solvent can be widely used herein as a reaction solvent, as long as it does not inhibit the reaction. Examples of such a solvent may include aprotic polar solvents such as DMF, DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

The molar ratio of the 1,1'-carbonyldiimidazole to the alcohol represented by the above general formula may be generally equal to 1 : 1 or

higher, preferably between 1 : 1 and 1.5 : 1, and more preferably between 1 : 1 and 1.1 : 1.

In the first step, the reaction temperature is generally 0°C to 100°C, preferably 0°C to 60°C, and
5 more preferably 10°C to 30°C. The reaction time is generally 30 minutes to 12 hours, preferably 1 to 6 hours, and more preferably 1 to 2 hours.

The molar ratio of the active intermediate to the starting material may be generally equal to 1 : 1
10 or higher, preferably between 1 : 1 and 1.5 : 1, and more preferably between 1 : 1 and 1.1 : 1.

In the second step, the reaction temperature is generally 0°C to 100°C, preferably 0°C to 60°C, and more preferably 10°C to 30°C. The reaction time is
15 generally 30 minutes to 12 hours, preferably 1 to 6 hours, and more preferably 1 to 2 hours.

The reaction mixture obtained by the above method (1) or (2) is, for example, cooled, and then its crude reaction product is separated therefrom by an
20 isolation operation such as filtration, concentration or extraction. Thereafter, the carbamate of interest can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

25 A compound having a heterocycle containing a nitrogen atom in a molecule thereof and comprising an $R^{32}R^{33}NCO$ -group (wherein R^{32} and R^{33} are the same as above) substituted on the nitrogen atom of the above

heterocycle selected from among the compounds of the present invention represented by general formula (1) can be produced by the reaction of a compound having a hydrogen atom substituted on the nitrogen atom of the
5 corresponding heterocycle.

For such a urea formation, for example, (1) a method using amine represented by a general formula $R^{32}R^{33}NH$ (wherein R^{32} and R^{33} are the same as above) and triphosgene, (2) a reaction of using amine represented
10 by the general formula $R^{32}R^{33}NH$ (wherein R^{32} and R^{33} are the same as above) and carbodiimidazole, and (3) a method using an isocyanate compound.

These reactions (1), (2) and (3) are carried out, for example, under the same reaction conditions
15 for the reactions with the compound (1-A-A1) as described in (1), (2) and (3) above.

The reaction mixture obtained by the above method (1), (2) or (3) is, for example, cooled, and then its crude reaction product is separated therefrom
20 by an isolation operation such as filtration, concentration or extraction. Thereafter, a compound of interest can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

25 As for the compounds of the present invention represented by general formula (1), a compound having a heterocycle containing a nitrogen atom in a molecule thereof and comprising an R^{38a} -group substituted on the

nitrogen atom of the above heterocycle (wherein R^{38a} represents a C1-C6 alkanoyl group, phenyl C2-C6 alkanoyl group (wherein, on the phenyl ring, at least one type of group selected from a group consisting of
 5 halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), phenoxy C2-C6 alkanoyl group wherein halogen atom may be substituted on the phenyl ring, phenylthio C2-C6
 10 alkanoyl group wherein halogen may be substituted on the phenyl ring, benzoyl group (wherein, on the phenyl ring, at least one type of group selected from a group consisting of halogen, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted
 15 or unsubstituted C1-C6 alkoxy group, and a C1-C6 alkylamino group may be substituted), 4-biphenyl-carbonyl group, pyridinylcarbonyl group, or phenyl C2-C6 alkenylcarbonyl group wherein halogen atom may be substituted on the phenyl ring), can be produced by
 20 reacting a compound comprising a hydrogen atom substituted on the nitrogen atom of the corresponding heterocycle, with carboxylic acid represented by a general formula $R^{38a}OH$ (wherein $R^{38a}OH$ is the same as above).

The above reaction can be carried out under
 25 the same conditions for the reaction of a compound (Ea-2) with a compound (18) represented by reaction scheme 19, which will be described later.

The reaction mixture obtained by the above

method is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, a compound of interest can be
5 isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

A compound having a heterocycle containing a nitrogen atom in a molecule thereof and comprising
10 $R^{39a}SO_2$ -substituted on the nitrogen atom of the above heterocycle (wherein R^{39a} represents a phenyl group which may be substituted by at least one group selected from a group consisting of a halogen atom and C1-C6 alkyl groups), selected from the compounds of the
15 present invention represented by general formula (1), can be produced by reacting a compound having a hydrogen atom substituted on the nitrogen atom of the corresponding heterocycle, with sulfonyl halide represented by a general formula $R^{39a}SO_2X_2$ (wherein R^{39a}
20 and X_2 are the same as above).

The above reaction can be carried out under the same conditions for the reaction of the compound (Fd-1) with a compound (15) represented by reaction scheme 18, which will be described later.

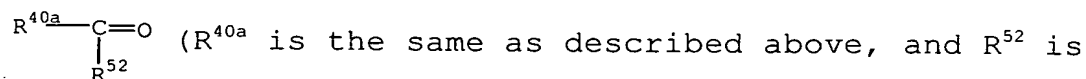
25 The reaction mixture obtained by the above method is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or

extraction. Thereafter, a compound of interest can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

5 As for the compounds of the present invention represented by general formula (1), a compound having a heterocycle containing a nitrogen atom in a molecule thereof and comprising an R^{40a} -CH- R^{52} group substituted on the nitrogen atom of the above heterocycle (wherein
10 R^{52} is the same as described later, and R^{40a} represents a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of halogen atom, a cyano group, a halogen substituted or unsubstituted C1-C6 alkyl group, a cyclohexyl group, an amino group
15 which may have a C1-C6 alkyl group as a substituent, a C1-C6 alkoxy carbonyl group, a phenoxy group, a phenyl C1-C6 alkyl group, a phenyl C2-C6 alkenyl group, a pyridyl group, an imidazolyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, and a
20 piperidinyl group may be substituted), 4-biphenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of halogen atom, a cyano group, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted
25 C1-C6 alkoxy group, and an amino group which may have a C1-C6 alkyl group as a substituent may be substituted), naphthyl group, furyl group, or thienyl group), can be produced by subjecting a compound comprising a hydrogen

atom substituted on the nitrogen atom of the corresponding heterocycle to a reductive alkylation reaction.

This reductive alkylation reaction is carried out, for example, by reacting a starting material with aldehyde or ketone represented by a general formula

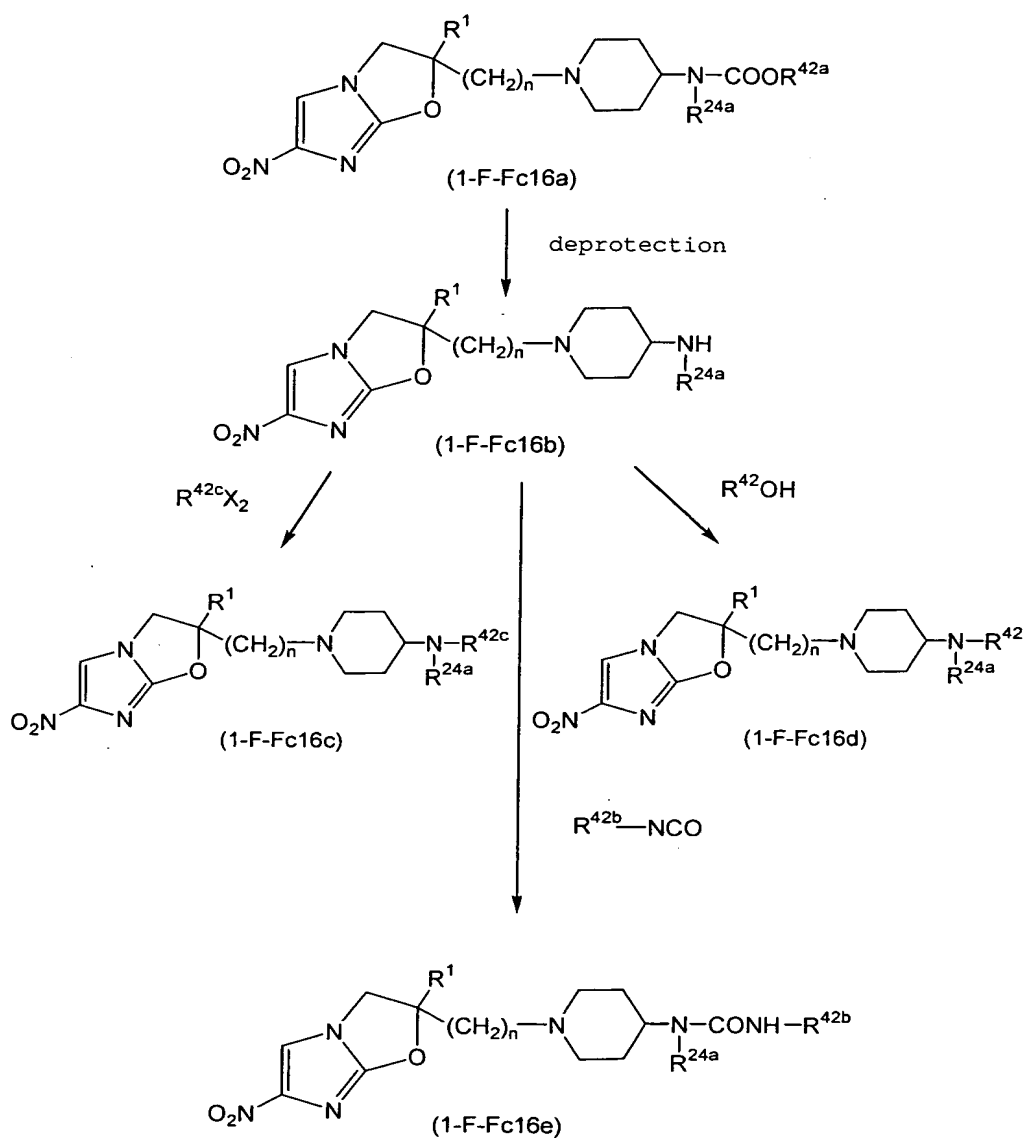


a hydrogen atom or C1-C6 alkyl group) in an appropriate solvent in the presence of the reducing agent.

This reaction can be carried out under the same condition for the reaction of a compound (E-2) with a compound (13) represented by reaction scheme 16, which will be described later.

The reaction mixture obtained by the above described method is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, a compound of interest can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

Reaction scheme 8



wherein R^1 , X_2 and n are the same as above, R^{24a} represents a group represented by each of (Fca1) to (Fca11), R^{42a} represents a C1-C6 alkyl group, R^{42} represents a group represented by (Fca5), (Fca6) or (Fca7), R^{42c} represents a group represented by (Fca2), (Fca3), (Fca4), (Fca8) or (Fca9), and R^{42b} represents a

phenyl group (wherein at least one selected from halogen substituted or unsubstituted C1-C6 alkyl groups may be substituted on the phenyl ring).

The reaction of converting a compound (1-F-Fc16a) into a compound (1-F-Fc16b) can be carried out under the same conditions for the reaction of converting a compound (E-1) into a compound (E-2) represented by reaction scheme 16, which is described later.

The thus obtained reaction mixture is concentrated, and if necessary, acid such as hydrochloric acid is added thereto for crystallization, so that a compound of interest can be isolated in a form of hydrochloride or trifluoroacetate by recrystallization or the like.

A compound (1-F-Fc16c) is produced by reacting the compound (1-F-Fc16b) with $R^{42c}X_2$. This reaction can be carried out under the same condition for the reaction of the compound (Fd-1) with the compound (15) represented by reaction scheme 18, which is described later.

A compound (1-F-Fc16d) is produced by reacting the compound (1-F-Fc16b) with $R^{42c}OH$. This reaction can be carried out under the same condition for the reaction of the compound (Ea-2) with the compound (18) represented by reaction scheme 19, which is described later.

The reaction mixture obtained by the above method is, for example, cooled, and then its crude

reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, a compound of interest can be isolated and purified from the reaction mixture by a
5 common purification operation such as column chromatography or recrystallization.

A compound (1-F-Fc16e) is produced by reacting the compound (1-F-Fc16b) with R^{42b} -NCO. This reaction can be carried out in the presence or absence
10 of, preferably in the absence of, a basic compound, in an appropriate inert solvent or without solvent.

Herein, as a solvent and a basic compound, there can be used the solvent and basic compound as follows.

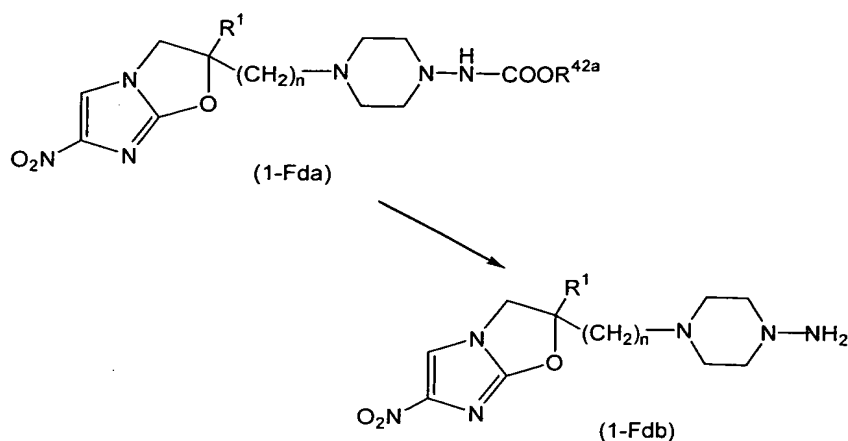
Examples of such a basic compound include: organic
15 bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo-[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO);

20 inorganic bases including carbonates such as sodium carbonate, potassium carbonate, sodium hydrogen-carbonate or potassium hydrogencarbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide or calcium hydroxide, potassium hydride,
25 sodium hydride, potassium, sodium, sodium amide, and metal alcoholates such as sodium methylate or sodium ethylate. Further, examples of a solvent include halogenated hydrocarbons such as chloroform,

dichloromethane, dichloroethane or carbon tetrachloride, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran or dimethoxyethane, 5 esters such as methyl acetate, ethyl acetate or isopropyl acetate, alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve or methyl cellosolve, acetonitrile, pyridine, acetone, water, aprotic polar solvents such 10 as N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide or hexamethylphosphoric acid triamide, and mixed solvents thereof. The molar ratio of the compound R^{42b} -NCO to the compound (1-F-Fc16b) may be generally between 1 : 1 and 5 : 1, and preferably 15 equal to 1 : 1 and 3 : 1. The reaction is carried out generally at 0°C to 200°C, and preferably at room temperature to 150°C, generally for 5 minutes to 30 hours. In the reaction, a boron compound such as boron trifluoride diethyl ether complex, or a halogenated 20 copper compound such as cuprous chloride may be added.

The thus obtained reaction mixture is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, a 25 compound of interest can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

Reaction scheme 9



wherein R^{42a} , R^1 and n are the same as above.

A compound (1-Fdb) is produced by deprotect-
 5 ing a compound (1-Fda). For example, the compound (1-Fda) is dissolved in an appropriate reaction solvent followed by hydrolysis with acid, so as to obtain the compound (1-Fdb).

Any reaction solvent can be widely used
 10 herein, as long as it does not inhibit the reaction. Examples of such a solvent include water, alcohol solvents such as methanol or ethanol, aprotic polar solvents such as DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or
 15 liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

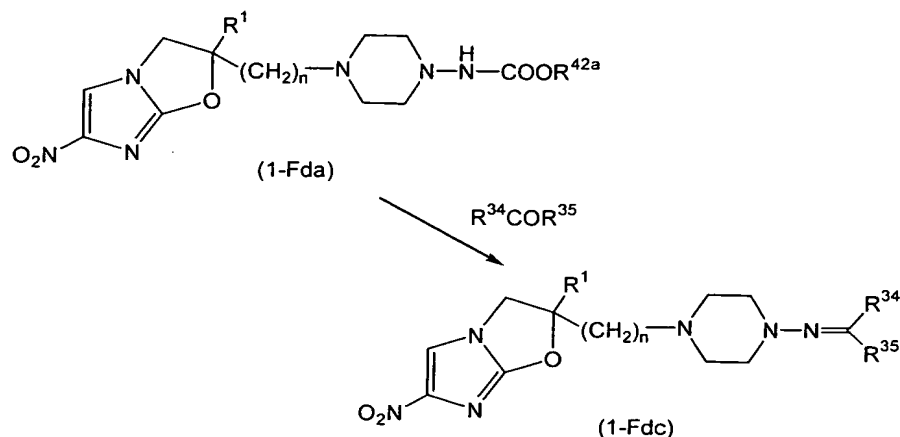
20 Examples of acid include inorganic acids such

as hydrochloric acid, hydrobromic acid or bromic acid, and organic acids such as acetic acid, trifluoroacetic acid or trichloroacetic acid. Of these, trifluoroacetic acid is advantageously used.

5 The molar ratio of such acid to the compound (1-Fda) is generally equal to 1 : 1 or higher, and preferably between 2 : 1 and 10 : 1. However, such acid may also be used a large excess amount as a reaction solvent. The reaction temperature is
10 generally room temperature to 100°C, but it may be appropriately adjusted depending on the type of the used acid. When trifluoroacetic acid is used, it is enough to set at room temperature. The reaction time is generally 1 to 24 hours, and preferably 1 to 12
15 hours.

 The thus obtained reaction mixture is concentrated, and if necessary, acid such as hydrochloric acid is added thereto for crystallization, so that the compound (1-Fdb) can be isolated in a form of
20 hydrochloride or trifluoroacetate by recrystallization or the like.

Reaction scheme 10



wherein R^{42a} , R^1 , n , R^{34} and R^{35} are the same as above.

A compound (1-Fdc) is produced by reacting the compound (1-Fda) with aldehyde or ketone
 5 represented by a general formula $\text{R}^{34}\text{COR}^{35}$ (wherein R^{34} and R^{35} are the same as above).

This reaction is carried out in the presence of acid in an appropriate solvent.

Any reaction solvent can be widely used
 10 herein, as long as it does not inhibit the reaction. Examples of such a solvent include water, alcohol solvents such as methanol or ethanol, aprotic polar solvents such as DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or
 15 liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and

mixed solvents thereof.

Examples of acid include inorganic acids such as hydrochloric acid, hydrobromic acid or bromic acid, and organic acids such as acetic acid, trifluoroacetic
5 acid or trichloroacetic acid. Of these, trifluoroacetic acid is advantageously used.

The molar ratio of such acid to the compound (1-Fda) is generally 0.5 : 1 or higher, and preferably between 0.5 : 1 and 1.5 : 1. However, such acid may
10 also be used a large excess amount as a reaction solvent.

The molar ratio of aldehyde or ketone to the compound (1-Fda) is generally between 0.9 : 1 and 3 : 1, preferably between 1 : 1 and 1.5 : 1, and more
15 preferably between 1 : 1 and 1.3 : 1.

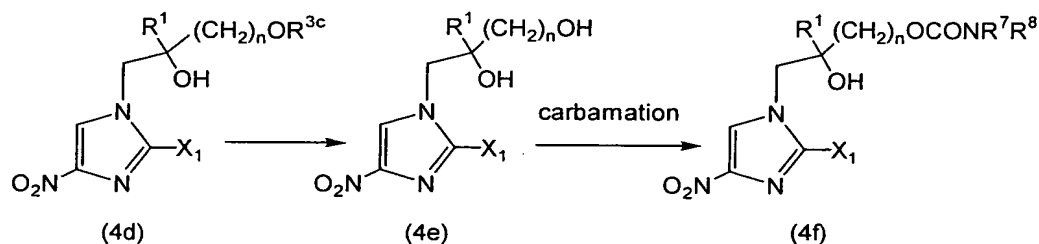
The reaction temperature is generally room temperature to 100°C, but it may be appropriately adjusted depending on the type of the used acid. The reaction time is generally 1 to 12 hours, and preferably
20 ably 1 to 3 hours.

The thus obtained reaction mixture is concentrated, and if necessary, acid such as hydrochloric acid is added thereto for crystallization, so that the compound (1-Fdc) can be isolated in a form of
25 hydrochloride or trifluoroacetate by recrystallization or the like.

Next, a method for producing a starting material and an intermediate used for production of the

compound of the present invention will be explained.

Reaction scheme 11



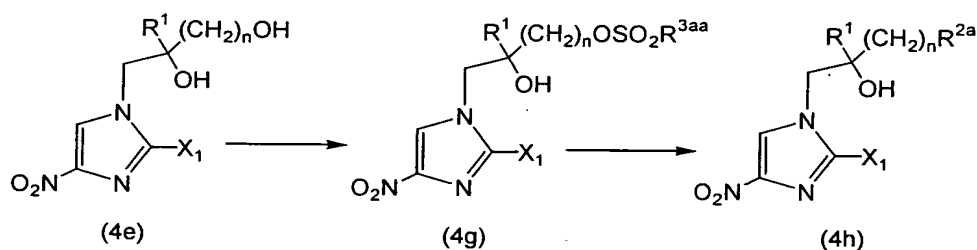
wherein R^1 , R^7 , R^8 , X_1 and n are the same as above, and
 5 R^{3c} represents a C1-C6 alkoxy-C1-C6 alkyl group, a C1-C6 alkanoyl group or a p-nitrobenzoyl group.

A reaction to lead from a compound (4d) into a compound (4e) is carried out, for example, under the same reaction conditions for the reaction to lead from
 10 the compound (1-A-A3) or compound (1-A-A9) into the compound (1-A-A1) as shown in reaction scheme 4. For example, in the case of the compound (4d) in which R^{3c} represents a C1-C6 alkoxy-C1-C6 alkyl group, it may be adequate to carry out the reaction under the same
 15 conditions for the reaction to lead from the compound (1-A-A3) into the compound (1-A-A1). In the case of the compound (4d) in which R^{3c} represents a C1-C6 alkanoyl or p-nitrobenzoyl group, it may be adequate to carry out the reaction under the same conditions for
 20 the reaction to lead from the compound (1-A-A9) into the compound (1-A-A1).

A reaction to lead from a compound (4e) into

a compound (4f) is carried out, for example, under the same reaction conditions for the reaction to lead from the compound (1-A-A1) into the compound (1-D) as shown in reaction scheme 7.

5 Reaction scheme 12

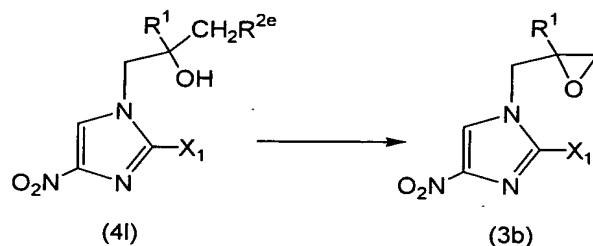


wherein R^1 , R^{2a} , R^{3aa} , X_1 and n are the same as above.

A reaction to lead from the compound (4e) into a compound (4g) is carried out, for example, under the same reaction conditions for the reaction to lead from the compound (1-A-A1) into the compound (1-A-A7) as shown in reaction scheme 5.

A reaction to lead from the compound (4g) into a compound (4h) is carried out, for example, under the same reaction conditions for the reaction to lead from the compound (1-A-A7) into the compound (1b) as shown in reaction scheme 6.

Reaction scheme 13



wherein R^1 and X_1 are the same as above, and R^{2e} represents a halogen atom, a C1-C6 alkylsulfonyloxy group or a phenylsulfonyloxy group which may have a C1-
 5 C6 alkyl group as a substituent on the phenyl ring.

A reaction to lead from a compound (4l) into a compound (3b) is carried out in an appropriate solvent in the presence of a basic compound.

Any solvent can be widely used herein, as
 10 long as it does not inhibit the reaction. Examples of such a solvent may include aprotic polar solvents such as DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene
 15 chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

The same basic compound as used in the
 20 reaction of the compound represented by the above general formula (2) with the compound represented by

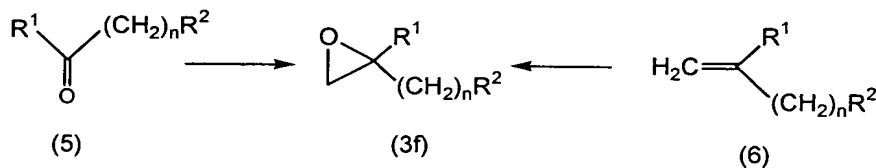
the above general formula (3a) can be used herein.

The molar ratio of such a basic compound to the compound (41) may be generally equal to 1 : 1 or higher, preferably between 1 : 1 and 5 : 1, and more
5 preferably between 1 : 1 and 2 : 1.

The reaction temperature for this reaction is generally 0°C to 150°C, preferably 0°C to 100°C, and more preferably 0°C to 60°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours, and
10 more preferably 1 to 4 hours.

The reaction mixture obtained by the above method is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extrac-
15 tion. Thereafter, the compound (3b) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

Reaction scheme 14



20 wherein R¹, R² and n are the same as above.

A reaction to lead from a compound (5) into a compound (3f) is carried out, for example, by treating the compound (5) with trimethylsulfoxonium iodide in an

appropriate solvent in the presence of a basic compound.

Any solvent can be widely used herein, as long as it does not inhibit the reaction. Examples of
5 such a solvent may include aprotic polar solvents such as DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, and mixed solvents thereof.

10 Examples of a basic compound may include sodium hydride, sodium amide, metal alcoholates such as sodium methoxide, sodium ethoxide or potassium tert-butoxide.

The molar ratio of such a basic compound to
15 the compound (5) may be generally equal to 1 : 1 or higher, preferably between 1 : 1 and 3 : 1, and more preferably between 1 : 1 and 1.5 : 1.

Moreover, the molar ratio of trimethylsulfoxonium iodide to the compound (5) may be generally
20 equal to 1 : 1 or higher, preferably between 1 : 1 and 3 : 1, and more preferably between 1 : 1 and 1.5 : 1.

The reaction temperature for this reaction is generally 0°C to 80°C, preferably 10°C to 50°C, and more preferably 20°C to 35°C. The reaction time is generally
25 1 to 24 hours, preferably 1 to 12 hours, and more preferably 1 to 4 hours.

The reaction mixture obtained by the above method is, for example, cooled, and then its crude

reaction product is separated therefrom by an isolation operation such as filtration, concentration or extraction. Thereafter, the compound (3f) can be isolated and purified from the reaction mixture by a common
5 purification operation such as column chromatography or recrystallization.

A reaction to lead from a compound (6) into the compound (3f) is carried out, for example, by treating the compound (6) with peroxide in an
10 appropriate solvent.

Any reaction solvent can be widely used herein, as long as it does not inhibit the reaction. Examples of such a solvent may include water, alcohol solvents such as methanol or ethanol, aprotic polar
15 solvents such as DMF, DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin, liquid paraffin or cyclohexane, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane,
20 dipropyl ether, diethyl ether or diglyme, and mixed solvents thereof.

Examples of peroxide include metachloro-
perbenzoic acid (mCPBA), perbenzoic acid, peracetic acid and hydrogen peroxide.

25 The molar ratio of such peroxide to the compound (6) may be generally between 1 : 1 and 2 : 1, preferably between 1 : 1 and 1.5 : 1, and more preferably between 1 : 1 and 1.3 : 1.

The reaction temperature for this reaction is generally 0°C to 80°C, preferably 0°C to 50°C, and more preferably 20°C to 35°C. The reaction time is generally 10 minutes to 24 hours, preferably 1 to 12 hours, and
5 more preferably 1 to 8 hours.

The reaction mixture obtained by the above method is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extrac-
10 tion. Thereafter, the compound (3f) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

For example, one type of the compounds (3f)
15 that is optically active is produced from the compound (6) as follows.

Such an optically active compound (3f) can be produced by what is called Sharpless epoxidation. This is to say, the compound can be produced by epoxidation
20 with cumene hydroperoxide or tert-butyl hydroperoxide, in the coexistence of Ti (O-iso-C₃H₇)₄ and optically active C1-C6 alkyl tartarate such as diethyl tartarate (D- or L-form) as catalysts, in the above reaction to lead from the compound (6) into the compound (3f).

25 Any solvent can be widely used herein, as long as it does not inhibit the reaction. Examples of such a solvent may include aprotic polar solvents such as acetonitrile, hydrocarbon solvents such as benzene,

toluene, xylene, tetralin, liquid paraffin or cyclohexane, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, and mixed solvents thereof.

The molar ratio of cumene hydroperoxide or tert-butyl hydroperoxide to the compound (6) may be generally between 0.1 : 1 and 2 : 1, preferably between 0.1 : 1 and 1.5 : 1, and more preferably between 0.1 : 1 and 1 : 1.

The molar ratio of Ti (O-iso-C₃H₇)₄ to the compound (6) may be generally between 0.1 : 1 and 2 : 1, preferably between 0.1 : 1 and 1.5 : 1, and more preferably between 0.1 : 1 and 1 : 1.

The molar ratio of optically active C1-C6 tartarates (D- or L-form) to the compound (6) may be generally between 1 : 1 and 2 : 1, preferably between 1 : 1 and 1.5 : 1, and more preferably between 1 : 1 and 1.3 : 1.

The reaction temperature for this reaction is generally -50°C to 30°C, preferably -20°C to 20°C, and more preferably -20°C to 5°C. The reaction time is generally 1 to 48 hours, preferably 4 to 24 hours, and more preferably 4 to 12 hours.

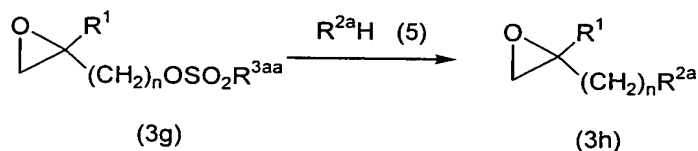
The compound (5) or (6), wherein R¹ and -(CH₂)_nR^{2a}, together with carbon atoms adjacent thereto, are bound with each other via nitrogen atoms to form a piperidine ring, is converted in the same manner as

stated above into a compound (compound (3c)), wherein R^1 and $-(CH_2)_nR^{2a}$, together with carbon atoms adjacent thereto, are bound with each other via nitrogen atoms to form a piperidine ring, in the compound (3f).

5 The reaction mixture obtained by the above method is, for example, cooled, and then its crude reaction product is separated therefrom by an isolation operation such as filtration, concentration or extrac-
 10 tion. Thereafter, the optically active compound (3f) can be isolated and purified from the reaction mixture by a common purification operation such as column chromatography or recrystallization.

 2,3-Dihydro-6-nitroimidazo[2,1-b]oxazole represented by the compound (1) of the present
 15 invention and its intermediates represented by above various reaction formulas include stereoisomers and optical isomers.

Reaction scheme 15

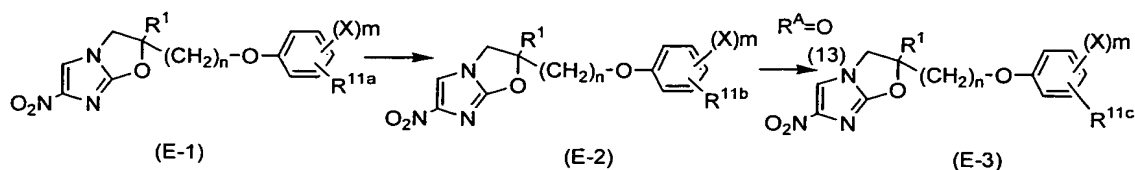


wherein R^{3aa} , R^1 , R^{2a} and n are the same as above.

20 A reaction to lead from a compound (3g) into a compound (3h) is carried out, for example, under the same reaction conditions for the reaction to lead from

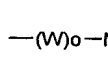
the compound (1-A-A7) into the compound (1b) as shown in reaction scheme 6.

Reaction scheme 16

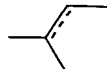


wherein R^1 , X , n and m are the same as above,

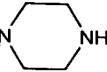
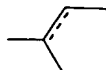
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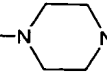
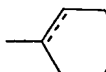
R^{11a} represents the group $-(W)_o-N$  $-R^{15a}$

(wherein W and o are the same as above, R^{15a} represents a C1-C20 alkoxy carbonyl group, with the exception that when W represents the group $C=O$, R^{15a} represents a C1-C6

alkoxy carbonyl group), or the group  $-R^{16a}$

10 (wherein R^{16a} represents a C1-C8 alkoxy carbonyl group),

R^{11b} represents the group $-(W)_o-N$  or group  ,

R^{11c} represents the group $-(W)_o-N$  $-R^{15b}$ or the group  $-R^{16b}$ (wherein each of R^{15b} and R^{16b}

15 represents a C3-C8 cycloalkyl group), and

R^A represents a C3-C8 cycloalkyl group.

The reaction to lead the compound (E-1) into the compound (E-2) can be carried out by the hydrolysis of the compound (E-1).

This hydrolysis reaction can be carried out in an appropriate solvent or without solvent in the presence of acid or a basic compound. Examples of the used solvent may include water, lower alcohols such as
5 methanol, ethanol, isopropanol or tert-butanol, ketones such as acetone or methylethylketone, ethers such as diethyl ether, dioxane, tetrahydrofuran, monoglyme or diglyme, fatty acids such as acetic acid or formic acid, esters such as methyl acetate or ethyl acetate,
10 halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, dimethyl sulfoxide, N,N-dimethylformamide, hexamethylphosphoric acid triamide, and mixed solvents thereof. Examples of acid may include inorganic acids such as
15 hydrochloric acid, sulfuric acid or hydrobromic acid, and organic acids including formic acid, acetic acid, trifluoroacetic acid or sulfonic acids such as p-toluenesulfonic acid. Examples of a basic compound may include carbonates such as sodium carbonate, potassium
20 carbonate, sodium hydrogencarbonate or potassium hydrogencarbonate, and metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide or lithium hydroxide. This reaction is carried out generally at 0°C to 200°C, and preferably at 0°C to
25 150°C, generally for 10 minutes to 30 hours.

The molar ratio of acid or basic compound to the compound (E-1) may be at least equal to 1 : 1, and preferably between 1 : 1 and 10 : 1. However, acid may

also be used a much higher amount as a reaction solvent.

After completion of the hydrolysis, the reaction may further be carried out in an appropriate solvent in the presence of a basic compound, generally at 0°C to 100°C, and preferably at room temperature to 70°C, approximately for 1 to 30 minutes, so as to complete the reaction. Herein, as a solvent and a basic compound, there can be used the solvent and basic compound as follows. Examples of such a basic compound include: organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO); inorganic bases including carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate or potassium hydrogencarbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide or calcium hydroxide, potassium hydride, sodium hydride, potassium, sodium, sodium amide, and metal alcoholates such as sodium methylate or sodium ethylate. Further, examples of a solvent include halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran or dimethoxy-

ethane, esters such as methyl acetate, ethyl acetate or isopropyl acetate, alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve or methyl cellosolve, acetonitrile, 5 pyridine, acetone, water, aprotic polar solvents such as N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide or hexamethylphosphoric acid triamide, and mixed solvents thereof.

The reaction of the compound (E-2) with the 10 compound (13) is carried out without solvent or in an appropriate solvent, in the presence of a reducing agent.

Examples of a solvent used herein may include water, lower alcohols such as methanol, ethanol, 15 isopropanol butanol, tert-butanol or ethylene glycol, acetonitrile, fatty acids such as formic acid, acetic acid or trifluoroacetic acid, ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme, aromatic hydrocarbons such as benzene, toluene or 20 xylene, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform or carbon tetrachloride, and mixed solvents thereof. Examples of a reducing agent include formic acid, fatty acid alkali metal salts such as sodium formate or sodium acetate, 25 and metal hydride reducing agents such as sodium borohydride, sodium cyanoborohydride, sodium triacetyloxy borohydride, lithium aluminum hydride or a mixture thereof, and catalytic hydrogenation reducing

agents such as palladium-black, palladium-carbon, platinum oxide, platinum black or Raney nickel.

When formic acid is used as a reducing agent, the reaction temperature is generally room temperature to 200°C, and preferably 50°C to 150°C. The reaction is carried out for 10 minutes to 10 hours. It may be preferable to use a much higher amount of formic acid to the compound (E-2).

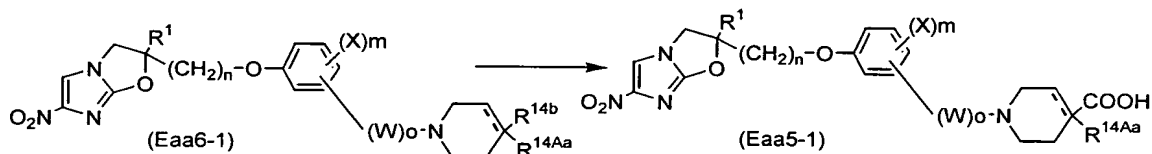
When a hydrogenation reducing agent is used, the reaction temperature is generally -80°C to 100°C, and preferably -80°C to 70°C. The reaction is carried out for 30 minutes to 100 hours. The hydrogenation reducing agent is used to the compound (E-2) at a molar ratio of generally between 1 : 1 and 20 : 1, and preferably between 1 : 1 and 6 : 1. In particular, when lithium aluminum hydride is used as a reducing agent, it is preferable to use, as a solvent, ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme, or aromatic hydrocarbons such as benzene, toluene or xylene. Moreover, amines such as trimethylamine, triethylamine, N-ethyldiisopropylamine may also be added for the reaction. Furthermore, molecular sieves such as molecular sieves 3A (MS-3A) or molecular sieves 4A (MS-4A) may also be added.

When a catalytic hydrogenation reducing agent is used, the reaction is carried out in hydrogen atmosphere, generally at normal atmospheric pressure to 20 atmospheric pressure, preferably at normal

atmospheric pressure to 10 atmospheric pressure, in the presence of a hydrogen provider such as formic acid, ammonium formate, cyclohexene or hydrated hydrazine, at a temperature of generally -30°C to 100°C , and preferably 0°C to 60°C . The reaction is generally carried out for 1 to 12 hours. Generally 0.1 to 40% by weight, and preferably 1 to 20% by weight of the catalytic hydrogenation reducing agent is used to the compound (E-2).

The compound (13) is used to the compound (E-2) at a molar ratio of generally at least equal to 1 : 1, and preferably equal to 1 : 1 or much higher.

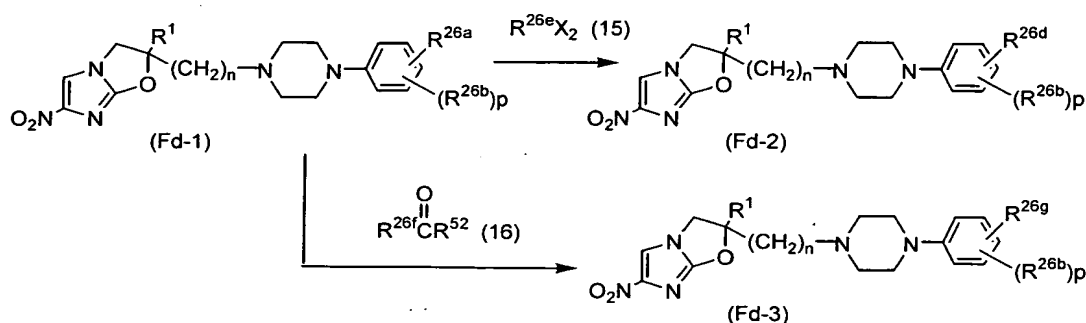
Reaction scheme 17



wherein R^1 , X , n , m , W and o are the same as above, $\text{R}^{14\text{b}}$ represents a C1-C6 alkoxy carbonyl group, and $\text{R}^{14\text{Aa}}$ is a hydrogen atom, a C1-C6 alkoxy group, a hydroxyl group or a phenyl group (phenyl group may have halogen atoms on the phenyl ring).

The reaction to lead the compound (Eaa 6-1) into the compound (Eaa 5-1) can be carried out under the same conditions for the reaction to lead the compound (E-1) into the compound (E-2) represented by the above reaction scheme 16.

Reaction scheme 18



wherein R¹, n and X₂ are the same as above, R⁵² is a hydrogen atom or C1-C6 alkyl group.

- 5 R^{26b} represents a halogen atom, a cyano group, amino group which may have a C1-C6 alkyl group as a substituent, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, a C1-C6 alkoxycarbonyl group, a
- 10 carboxyl group, a phenoxy group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be
- 15 substituted as a substituent), an amino C1-C6 alkyl group (wherein, on the amino group, at least one group selected from a group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a
- 20 halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as

a substituent) may be substituted as a substituent), or
 a phenyl C1-C6 alkoxy group (wherein, on the phenyl
 ring, at least one group selected from a group
 consisting of a halogen atom, a halogen substituted or
 5 unsubstituted C1-C6 alkyl group, and a halogen
 substituted or unsubstituted C1-C6 alkoxy group may be
 substituted as a substituent),

p represents an integer of 0 to 4,

R^{26a} represents the group $-NHR^{26h}$ (wherein R^{26h}
 10 represents a hydrogen atom or a C1-C6 alkyl group), or
 the group $-W_1-NHR^{26c}$ (wherein W_1 is a C1-C6 alkylene
 group, R^{26c} represents a hydrogen atom, a C1-C6 alkyl
 group or a phenyl group (wherein, on the phenyl ring,
 at least one group selected from a group consisting of
 15 a halogen atom, a halogen substituted or unsubstituted
 C1-C6 alkyl group, and a halogen substituted or
 unsubstituted C1-C6 alkoxy group may be substituted as
 a substituent)),

R^{26d} represents the group $-N(R^{26e'})R^{26h}$ or the
 20 group $-W_1-N(R^{26c})R^{26e}$,

R^{26e} represents a phenyl group (wherein, on the
 phenyl ring, at least one group selected from a group
 consisting of a halogen atom, a halogen substituted or
 unsubstituted C1-C6 alkyl group, and a halogen
 25 substituted or unsubstituted C1-C6 alkoxy group may be
 substituted as a substituent) or a C1-C6 alkyl group,

$R^{26e'}$ represents a C1-C6 alkyl group,

R^{26f} represents a C1-C6 alkyl group, and

R^{26g} represents the group $-N(R^{26h})\underline{CH(R^{52})R^{26f}}$ or the group $-W_1-N(R^{26c})\underline{CH(R^{52})R^{26f}}$, provided that the total number of carbon atoms of the underlined portions is not greater than 6.

5 The reaction of the compound (Fd-1) with the compound (15) is generally carried out in an appropriate solvent in the presence or absence of a basic compound.

 Examples of an inert solvent used herein may
 10 include aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform or carbon tetrachloride, lower alcohols such
 15 as methanol, ethanol, isopropanol, butanol, tert-butanol or ethylene glycol, fatty acids such as acetic acid, esters such as ethyl acetate or methyl acetate, ketones such as acetone or methylethylketone, acetonitrile, pyridine, dimethylsulfoxide, N,N-
 20 dimethylformamide or hexamethylphosphoric acid triamide, and mixed solvents thereof. Examples of a basic compound may include carbonates such as sodium carbonate, potassium carbonate, sodium hydrogen-carbonate, potassium hydrogencarbonate or cesium
 25 carbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide or calcium hydroxide, sodium hydride, potassium hydride, potassium, sodium, sodium amide, metal alcoholates such as sodium methylate,

sodium ethylate, sodium n-butoxide, organic bases such as pyridine, imidazole, N-ethyldiisopropylamine, dimethylaminopyridine, triethylamine, trimethylamine, dimethylaniline, N-methylmorpholine, 1,5-

5 diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) or 1,4-diazabicyclo[2.2.2]-octane (DABCO), and mixtures thereof. The compound (15) may be used to the compound (Fd-1) at a molar ratio of at least equal to 1 : 1, and preferably

10 between 1 : 1 and 10 : 1. The basic compound may be used to the compound (Fd-1) at a molar ratio of at least equal to 1 : 1, and preferably between 1 : 1 and 10 : 1. The reaction is carried out generally at 0°C to 200°C, and preferably at 0°C to 150°C. The reaction is

15 generally carried out for 5 minutes to 80 hours.

Alkali metal halides such as sodium iodide or potassium iodide may be added to the reaction system, or a phase-transfer catalyst may also be added thereto. Examples of such a phase-transfer catalyst include:

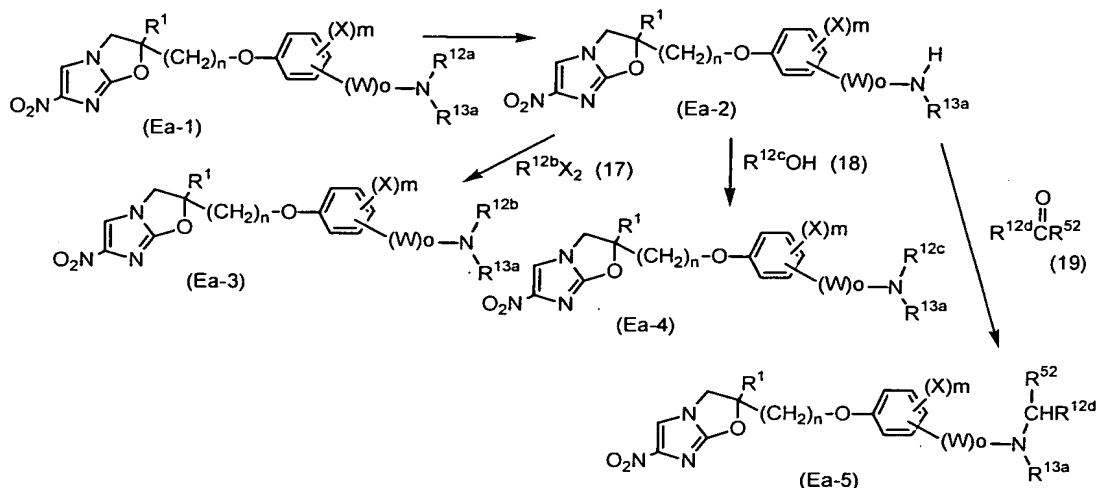
20 quaternary ammonium salts, in which a group selected from a group consisting of a linear or branched alkyl group containing 1 to 18 carbon atoms, a phenyl C1-C6 alkyl group, and a phenyl group is substituted, such as tetrabutylammonium chloride, tetrabutylammonium

25 bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium bisulfite, tributylmethyammonium chloride, tributylbenzylammonium chloride, tetrapentyl-

ammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyldimethyloctyl-ammonium chloride, methyltrihexylammonium chloride, benzyldimethyloctadecanylammonium chloride, 5 methyltridecanylammonium chloride, benzyltripropyl-ammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, or tetramethylammonium chloride; phosphonium salts such as tetrabutylphosphonium chloride, in which 10 a linear or branched alkyl group containing 1 to 18 carbon atoms is substituted; and pyridinium salts such as 1-dodecanylpseudinium chloride, in which a linear or branched alkyl group containing 1 to 18 carbon atoms is substituted. The phase-transfer catalyst may be used 15 to the compound (Fd-1) at a molar ratio of generally between 0.1 : 1 and 1 : 1, and preferably between 0.1 : 1 and 0.5 : 1.

The reaction of the compound (Fd-1) with the compound (16) can be carried out under the same 20 conditions for the above reaction of the compound (E-2) with the compound (13) represented by the above reaction scheme 16.

Reaction scheme 19



wherein R^1 , n , W , X , m , o , R^{52} and X_2 are the same as above,

- 5 R^{12a} represents a C1-C6 alkoxy carbonyl group,
 R^{13a} represents a hydrogen atom, a C1-C6 alkyl group, a C1-C6 alkanoyl group, a C1-C6 alkoxy carbonyl group, a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one of group selected from a
- 10 group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, and a phenoxy group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen
- 15 atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent) may be substituted, and a C1-C6 alkoxyimino group may

be substituted for the alkyl portion), a phenyl group (wherein, on the phenyl ring, at least one of group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), a benzoyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), a pyridyl group (wherein, on the pyridine ring, at least one of halogen atom may be substituted as a substituent), phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), or a benzoyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent),

25 R^{12b} represents a C1-C6 alkyl group, a C1-C6 alkoxycarbonyl group, a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a

halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, and a phenoxy group (wherein, on the phenyl ring, at least one group selected from a group

5 consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), may be substituted as a substituent, and a C1-C6 alkoxyimino group may be

10 substituted for the alkyl portion), a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy

15 group may be substituted as a substituent), a pyridyl group (wherein, on the pyridine ring, at least one of halogen atom may be substituted as a substituent), a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of

20 a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), or a benzoyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group

25 selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent),

R^{12c} represents a C1-C6 alkanoyl group, or a benzoyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent),

R^{12d} represents a hydrogen atom, a C1-C6 alkyl group, a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, and a phenoxy group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent) may be substituted), a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, and a phenoxy group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent) may be

substituted), a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a
 5 halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), or a benzoyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6
 10 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), and

in the group $-(W)O-N(R^{13a})\underline{CH(R^{52})R^{12d}}$ in general formula (Ea-5), the total number of carbon atoms of the
 15 underlined portion is not greater than 6.

The reaction to lead the compound (Ea-1) into the compound (Ea-2) can be carried out under the same conditions for the reaction to lead the compound (E-1) into the compound (E-2) represented by the above
 20 reaction scheme 16.

The reaction of the compound (Ea-2) with the compound (17) can be carried out under the same conditions for the reaction of the compound (Fd-1) with the compound (15) represented by the above reaction
 25 scheme 18.

The reaction of the compound (Ea-2) with the compound (18) is carried out by reacting the compound (Ea-2) with carboxylic acid of the compound (18) by a

common amide bond formation reaction. Conditions for a known amide bond formation reaction can be easily applied herein. Examples of such an amide bond formation reaction include (a) mixed acid anhydride method, 5 that is, a method of reacting carboxylic acid (18) with alkyl haloformate to obtain a mixed acid anhydride and reacting the mixed acid anhydride with amine (Ea-2), (b) active ester method, that is, a method of converting carboxylic acid (18) into active ester such as 10 phenyl, p-nitrophenyl ester, N-hydroxy succinic acid imide ester or 1-hydroxybenzotriazole ester, or into active amide such as benzoxazoline-2-thione, and then reacting this with amine (Ea-2), (c) carbodiimide method, that is, a method of carrying out the 15 condensation reaction of carboxylic acid (18) with amine (Ea-2) in the presence of an activator such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC) or carbonyldiimidazole, and (d) other methods including a method of converting 20 carboxylic acid (18) into carboxylic anhydride by using a dehydrator such as acetic anhydride and reacting the carboxylic anhydride with amine (Ea-2), a method of reacting ester of carboxylic acid (18) and lower alcohol with amine (Ea-2) at high pressure and high 25 temperature, and a method of reacting acid halide of carboxylic acid (18), i.e., carboxylic acid halide, with amine (Ea-2).

The mixed acid anhydride used in (a) mixed

acid anhydride method as described above is obtained by a common Schotten-Baumann reaction. The mixed acid anhydride is reacted with amine (Ea-2) generally without subjecting to isolation, so as to produce the compound of the present invention represented by general formula (Ea-4). The above Schotten-Baumann reaction is carried out in the presence of a basic compound. Compounds that are commonly used for the Schotten-Baumann reaction can be used herein as basic compounds. Examples of such a basic compound include: organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO); inorganic bases including carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate or potassium hydrogencarbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide or calcium hydroxide, potassium hydride, sodium hydride, potassium, sodium, sodium amide, and metal alcoholates such as sodium methylate or sodium ethylate. The reaction is carried out generally at -20°C to 100°C, and preferably at 0°C to 50°C. The reaction time is generally 5 minutes to 10 hours, and preferably 5 minutes to 2 hours. The reaction of the obtained mixed acid anhydride with amine (Ea-2) is carried out

generally at -20°C to 150°C , and preferably at 10°C to 50°C . The reaction time is generally 5 minutes to 10 hours, and preferably 5 minutes to 5 hours. The mixed acid anhydride method is generally carried out in a solvent. Any solvent that is commonly used for the mixed acid anhydride method can be used herein. Examples of such a solvent include halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran or dimethoxyethane, esters such as methyl acetate, ethyl acetate or isopropyl acetate, aprotic polar solvents such as N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide or hexamethylphosphoric acid triamide, and mixed solvents thereof. Examples of alkyl haloformate used for the mixed acid anhydride method include methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, and isobutyl chloroformate. The molar ratio among carboxylic acid (18), alkyl haloformate and amine (Ea-2) may be generally equal to 1 : 1. Each of alkyl haloformate and carboxylic acid (18) can also be used to amine (Ea-2) within the molar range between 1 : 1 and 1.5 : 1.

The above method (c) involving the condensation reaction in the presence of the above activator can be carried out in an appropriate solvent in the

presence or absence of a basic compound. As a solvent and a basic compound used herein, any solvent used in the reaction of carboxylic acid halide with amine (Ea-2) described as above in (d) other methods can be used.

5 The molar ratio of the activator to the compound (Ea-2) may be at least equal to 1 : 1, and preferably between 1 : 1 and 5 : 1. When WSC is used as an activator, the reaction advantageously proceeds if 1-hydroxy-benzotriazole is added into the reaction system. The

10 reaction is carried out generally at -20°C to 180°C, and preferably at 0°C to 150°C. The reaction time is generally 5 minutes to 90 hours.

When the method of reacting carboxylic acid halide with amine (Ea-2) is adopted from (d) other

15 methods described above, the reaction is carried out in the presence of a basic compound in an appropriate solvent. Known basic compounds can be widely used herein. For example, any basic compound used in the above Schotten-Baumann reaction can be used. Examples

20 of the used solvent may include alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve or methyl cellosolve, acetonitrile, pyridine, acetone, water, as well as solvents used for the above mixed acid

25 anhydride method. The molar ratio of amine (Ea-2) to carboxylic acid halide is not particularly limited, but it may be appropriately selected from a wide range. The molar ratio of these compounds may be generally at

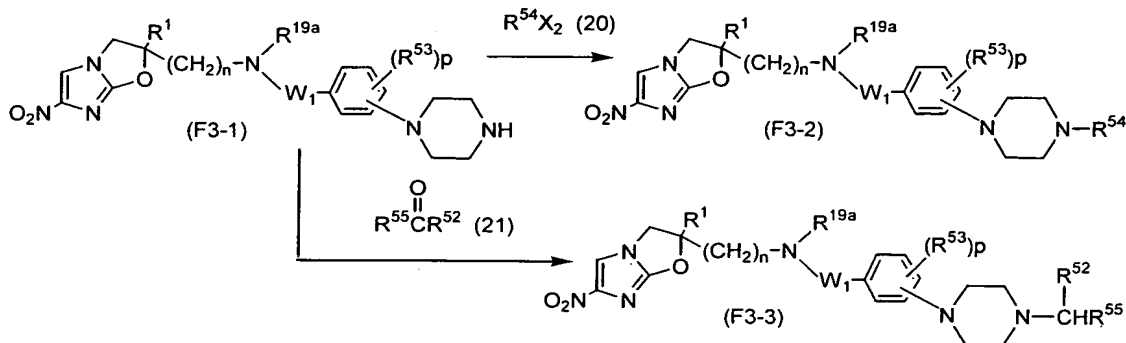
least equal to 1 : 1, and preferably between 1 : 1 and 1 : 5. The reaction is carried out generally at -20°C to 180°C, and preferably at 0°C to 150°C. The reaction time is generally 5 minutes to 50 hours.

5 The amide bond formation reaction represented by the above reaction scheme-19 can also be carried out by reacting carboxylic acid (18) with amine (Ea-2) in the presence of a phosphorus condensing agent such as diphenylphosphinic chloride, phenyl-N-phenyl
10 phosphoramidate chloridate, diethyl chlorophosphate, diethyl cyanophosphate, azide diphenyl phosphate, or bis(2-oxo-3-oxazolidinyl)phosphinic chloride.

 This reaction is carried out in the presence of a solvent and a basic compound that are used for the
15 above method of reacting carboxylic acid halide with amine (Ea-2), generally at -20°C to 150°C, and preferably at 0°C to 100°C. The reaction time is generally 5 minutes to 30 hours. Each of the condensing agent and the carboxylic acid (18) is used to amine (Ea-2) at a
20 molar ratio of at least equal to 1 : 1, and preferably between 1 : 1 and 2 : 1.

 The reaction of the compound (Ea-2) with the compound (19) can be carried out under the same conditions for the reaction of the compound (E-2) with
25 the compound (13) represented by the above reaction scheme 16.

Reaction scheme 20



wherein R^1 , n , R^{52} , p , W_1 and X_2 are the same as above,

5 R^{19a} represents a group represented by each of (F1) to (F11).

R^{53} represents a phenoxy group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, an amino group which may have, as a substituent, a group selected from a group consisting of a C1-C6 alkyl group and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a

10 substituted or unsubstituted C1-C6 alkyl group, and a

15

20

halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), a piperazinyl group (wherein, on the piperazine ring, at least one group selected from a group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group) may be substituted as a substituent or a piperidinyl group (wherein, on the piperidine ring, at least one amino group may be substituted, as a substituent, and on the amino group, at least one group selected from a group consisting of a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted unsubstituted C1-C6 alkoxy group may be substituted as a substituent) and a C1-C6 alkyl group may be substituted),

R^{54} represents a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent),

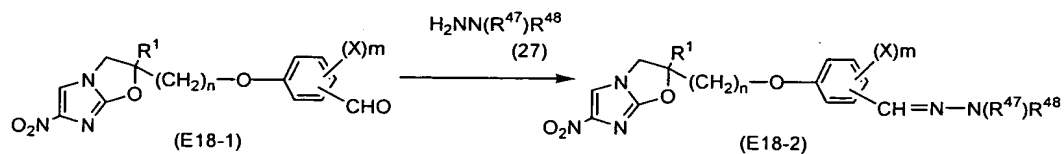
R^{55} represents a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a

halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), or phenyl group (wherein, on the phenyl ring, at least one group
 5 selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), and
 the total number of carbon atoms of the group
 10 $\text{CH}(\text{R}^{52})\text{R}^{55}$ in general formula (F3-3) is not greater than 6.

The reaction of the compound (F3-1) with the compound (20) can be carried out under the same conditions for the reaction of the compound (Fd-1) with
 15 the compound (15) represented by the above reaction scheme 18.

The reaction of the compound (F3-1) with the compound (21) can be carried out under the same conditions for the reaction of the compound (E-2) with
 20 the compound (13) represented by the above reaction scheme 16.

Reaction scheme 21



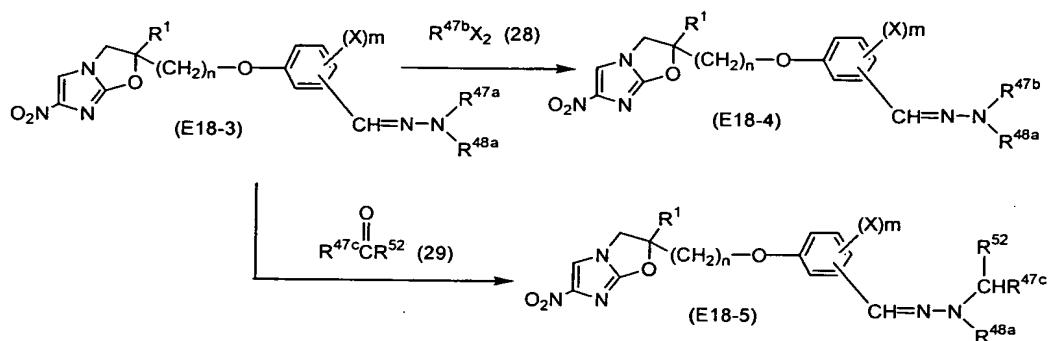
wherein R^1 , n , X , R^{47} , R^{48} and m are the same as above.

The reaction of the compound (27) with the compound (E18-1) can be carried out in an appropriate inert solvent in the presence or absence of a basic compound.

5 Examples of the used basic compound may include inorganic basic compounds such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate or potassium carbonate, fatty acid alkali metal salts such as sodium acetate, and organic
10 bases such as piperidine, triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) or 1,4-diazabicyclo[2.2.2]-
15 octane (DABCO). Any inert solvent can be used herein, as long as it does not affect the reaction. Examples of such a solvent include water, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme or
20 diglyme, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform or carbon tetrachloride, lower alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol or ethylene glycol, fatty acids such as acetic acid, esters such as ethyl
25 acetate or methyl acetate, ketones such as acetone or methylethylketone, acetonitrile, pyridine, dimethylsulfoxide, N,N-dimethylformamide, hexamethylphosphoric acid triamide, and mixed solvents thereof. The molar

ratio of the compound (27) to the compound (E18-1) may be generally at least equal to 1 : 1, and preferably between 1 : 1 and 5 : 1. The reaction temperature is generally room temperature to 200°C, and preferably room temperature to 150°C. The reaction time is generally 5 minutes to 30 hours.

Reaction scheme 22



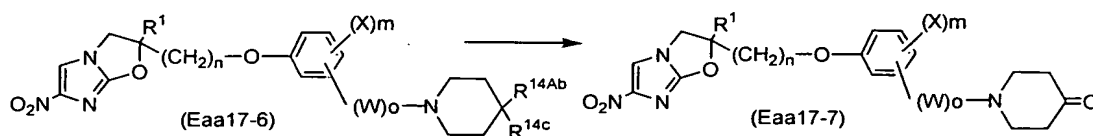
wherein R^1 , n , X , m , X_2 and R^{52} are the same as
 10 above,

R^{47a} represents a hydrogen atom,

R^{48a} represents a hydrogen atom, a C1-C6 alkyl group, a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a
 15 halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), or a pyridyl group (wherein, on the pyridine ring, at least one halogen substituted or
 20 unsubstituted C1-C6 alkyl group may be substituted as a substituent),

- R^{47b} represents a C1-C6 alkyl group; a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent); or a pyridyl group (wherein, on the pyridine ring, at least one halogen substituted or unsubstituted C1-C6 alkyl group may be substituted as a substituent), and
- R^{47c} represents a hydrogen atom or a C1-C6 alkyl group, provided that, in the group $-CH=N-N(R^{48a})\underline{CH(R^{52})R^{47c}}$ in general formula (Ea 18-5), the total number of carbon atoms of the underlined portion is not greater than 6.
- The reaction of the compound (E18-3) with the compound (28) can be carried out under the same conditions for the reaction of the compound (Fd-1) with the compound (15) represented by the above reaction scheme 18.
- The reaction of the compound (E18-3) with the compound (29) can be carried out under the same conditions for the reaction of the compound (E-2) with the compound (13) represented by the above reaction scheme 16.

Reaction scheme 23

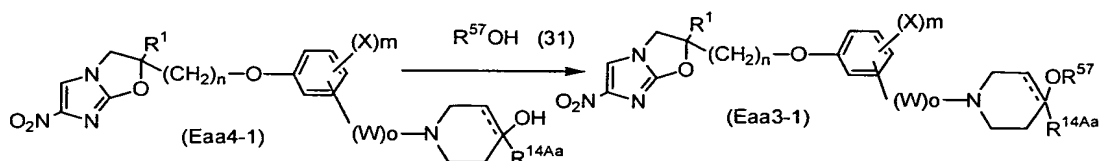


wherein R^1 , n , X , m , W and o are the same as above,

each of R^{14Ab} and R^{14c} represents a C1-C6 alkoxy group.

The reaction to lead the compound (Eaa 17-6) into the compound (Eaa 17-7) can be carried out under the same conditions for the reaction to lead the compound (E-1) into the compound (E-2) represented by the above reaction scheme 16.

Reaction scheme 24



wherein R^1 , n , X , m , W , o and R^{14Aa} are the same as above,

the dotted line on the piperidine ring represents that the bond may be a double bond, and when the dotted line represents a double bond, it means that the hydroxyl group is substituted,

R^{57} represents a phenyl group (wherein, on the

phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, a C1-C4

5 alkylenedioxy group, a C1-C6 alkoxy carbonyl group, a cyano group, a C2-C6 alkenyl group, a nitro group, a phenyl group, an amino group which may have, as a substituent, a group selected from a group consisting of a phenyl group, a C1-C6 alkyl group, a carbomoyl

10 group and a C1-C6 alkanoyl group, a C1-C6 alkanoyl substituted C1-C6 alkyl group, a hydroxyl group, a C1-C6 alkoxy carbonyl substituted C1-C6 alkyl group, phenyl C1-C6 alkyl group, a C1-C6 alkanoyl group, a C1-C6 alkylthio group, a 1,2,4-triazolyl group, an isoxazolyl

15 group, an imidazolyl group, a benzothiazolyl group, a 2H-benzotriazolyl group, a pyrrolyl group, a benzoxazolyl group, a piperazinyl group (wherein, on the piperazine ring, at least one group selected from a group consisting of a C1-C6 alkoxy carbonyl group and a

20 phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one of group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be

25 substituted as a substituent) may be substituted as a substituent), a piperidinyl group (wherein, on the piperidine ring, at least one amino group may be substituted as a substituent, and on the amino group,

at least one group selected from a group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent) may be substituted as a substituent) and a carbamoyl group may be substituted as a substituent).

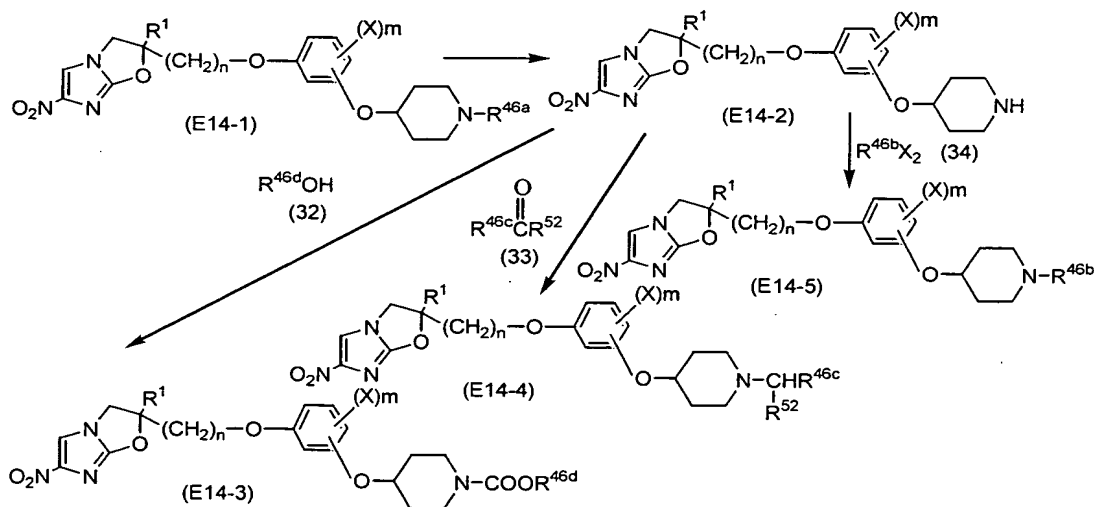
10 The reaction of the compound (Eaa 4-1) with the compound (31) can be carried out in an appropriate solvent in the presence of a condensing agent.

 Herein, there can be used the solvent mentioned below. Examples of such a solvent include
15 halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran or dimethoxyethane,
20 esters such as methyl acetate, ethyl acetate or isopropyl acetate, alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve or methyl cellosolve, acetonitrile, pyridine, acetone, water, aprotic polar solvents such
25 as N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide or hexamethylphosphoric acid triamide, and mixed solvents thereof.

 Examples of the condensing agent used herein

may include azocarboxylates such as diethyl azodicarboxylate or tert-butyl azodicarboxylate, and phosphorus compound mixtures such as triphenylphosphine or triphenylphosphine polymer supported. This reaction is carried out generally at 0°C to 200°C, and preferably at 0°C to 150°C. The reaction is generally carried out for 1 to 10 hours. The molar ratio of the condensing agent to the compound (Eaa 4-1) may be at least equal to 1 : 1, and preferably between 1 : 1 and 3 : 1. The molar ratio of the compound (31) to the compound (Eaa 4-1) may be at least equal to 1 : 1, and preferably between 1 : 1 and 2 : 1.

Reaction scheme 25



wherein R^1 , n , X , m , X_2 and R^{52} are the same as above,

R^{46a} represents a C1-C6 alkoxy carbonyl group,
 R^{46b} represents a phenyl group (wherein, on the

phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), a phenyl C1-C6 alkoxycarbonyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), or a C1-C6 alkoxycarbonyl group,

R^{46c} represents a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), or a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), and

R^{46d} represents a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent), or a C1-C6 alkyl group.

The reaction to lead the compound (E14-1) into the compound (E14-2) can be carried out under the same conditions for the reaction to lead the compound (E-1) into the compound (E-2) represented by the above reaction scheme 16.

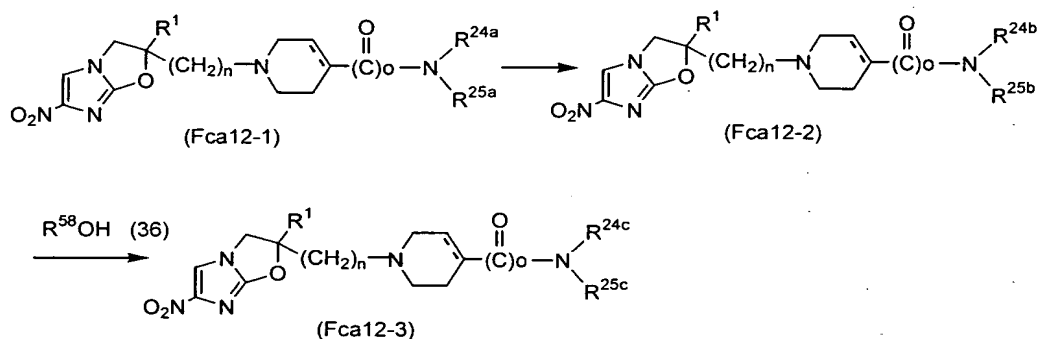
The reaction of the compound (E14-2) with the compound (34) can be carried out under the same conditions for the reaction of the compound (Fd-1) with the compound (15) represented by the above reaction scheme 18.

The reaction of the compound (E14-2) with the compound (33) can be carried out under the same conditions for the reaction of the compound (E-2) with the compound (13) represented by the above reaction scheme 16.

The reaction of the compound (E14-2) with the compound (32) can be carried out in an appropriate solvent in the presence of a condensing agent. Any solvent can be used herein, which is used in the method of the reactions of the compound (Eaa 4-1) with the compound (31) represented by the above reaction scheme 24. N,N'-carbonyldiimidazole is an example of the

condensing agent used herein. Each of the compound (32) and the condensing agent is used to the compound (E14-2) at a molar ratio of at least equal to 1 : 1, and preferably between 1 : 1 and 2 : 1. This reaction is carried out generally at 0°C to 150°C, and preferably at 0°C to 100°C, approximately for 1 to 30 hours.

Reaction scheme 26



wherein R¹, n and o are the same as above, R^{24a} and R^{25a} form a piperazine ring through a nitrogen atom adjacent thereto, and the piperazine ring, which R^{24a} and R^{25a} form, may have, as a substituent, at least one substituent described as above, for the substituents of the 5 to 6-membered saturated heterocycle that R²⁴ and R²⁵ form through nitrogen atoms adjacent thereto, and the piperazine ring that R^{24a} and R^{25a} form has a C1-C6 alkoxycarbonyl group on the nitrogen atom on the piperazine ring, R⁵⁸ represents a phenyl group (wherein, on the phenyl ring, at least one group selected from a group

consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent),

5 R^{24b} and R^{25b} form a piperazine ring through a nitrogen atom adjacent thereto, and the piperazine ring, which R^{24b} and R^{25b} form, may have, as a substituent at least one substituent described as above, for the substituent of the 5 to 6-membered saturated

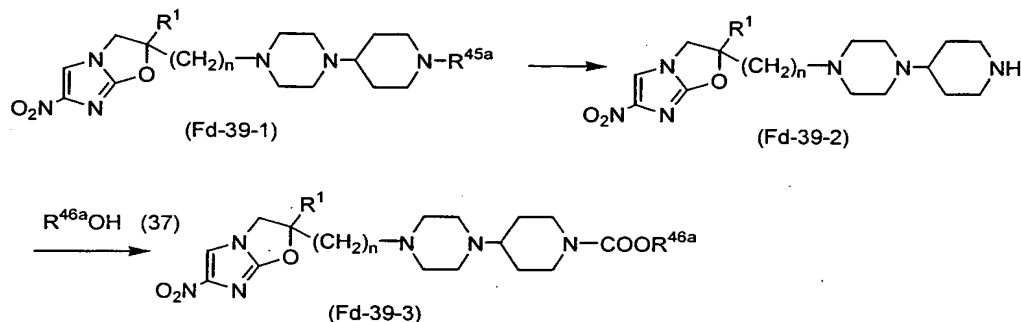
10 heterocycle that R^{24} and R^{25} form through nitrogen atoms adjacent thereto, and the piperazine ring that R^{24b} and R^{25b} form has a hydrogen atom on the nitrogen atom on the piperazine ring, and

R^{24c} and R^{25c} form a piperazine ring through a
15 nitrogen atom adjacent thereto, and the piperazine ring, which R^{24c} and R^{25c} form, may have, as a substituent, at least one substituent described as above, for the substituents of the 5 to 6-membered saturated heterocycle that R^{24} and R^{25} form through
20 nitrogen atoms adjacent thereto, and the piperazine ring that R^{24c} and R^{25c} form has a phenyl C1-C6 alkoxy carbonyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted
25 C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent) on the nitrogen atom on the piperazine ring.

The reaction to lead the compound (Fca 12-1) into the compound (Fca 12-2) can be carried out under the same conditions for the reaction to lead the compound (E-1) into the compound (E-2) represented by
 5 the above reaction scheme 16.

The reaction of the compound (Fca 12-2) with the compound (36) can be carried out under the same conditions for the reaction of the compound (E14-2) with the compound (32) represented by the above
 10 reaction scheme 25.

Reaction scheme 27



wherein R^1 and n are the same as above,
 R^{45a} represents a C1-C6 alkoxy carbonyl group,
 15 and
 R^{46a} represents a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen
 20 substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent).

The reaction to lead the compound (Fd-39-1)

into the compound (Fd-39-2) can be carried out under the same conditions for the reaction to lead the compound (E-1) into the compound (E-2) represented by the above reaction scheme 16.

5 The reaction of the compound (Fd-39-2) with the compound (37) can be carried out under the same conditions for the reaction of the compound (E14-2) with the compound (32) represented by the above reaction scheme 25.

10 The compound of the present invention includes a pharmaceutically acceptable salt. Examples of such a salt include inorganic salts such as hydrochloride, hydrobromide, nitrate, sulfate or phosphate, and organic salts such as methanesulfonate, p-
15 toluenesufonate, acetate, citrate, tartrate, maleate, fumarate, malate or lactate.

Next, a medical preparation containing the compound of the present invention as an active ingredient will be explained.

20 The above medical preparation is obtained by preparing the compound of the present invention in the form of a common medical preparation. It is prepared using commonly used diluents or excipients such as a filler, expander, binder, wetting agent, disintegrator,
25 surfactant or lubricant.

Such a medical preparation can be selected from among various forms, depending on therapeutic purposes. Typical examples of a preparation form

include a tablet, pill, powder, liquid, suspension, emulsion, granule, capsule, suppository, and injection (liquid, suspension, etc.)

Known carriers can be widely used in making the medical preparation in a tablet form. Examples of such a carrier include excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaoline or crystalline cellulose; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate or polyvinylpyrrolidone; disintegrators such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen- carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceride stearate, starch or lactose; disintegration controllers such as sucrose, stearin, cacao butter or hydrogenated oil; absorption enhancers such as quaternary ammonium base or sodium lauryl sulfate, humectants such as glycerin or starch, adsorbents such as starch, lactose, kaoline, bentonite or colloidal silica, and lubricants such as purified talc, stearate, boric acid powder or polyethylene glycol.

Moreover, such tablets can be prepared as tablets with common tablet coating, such as a sugar coated tablet, gelatin coated tablet, enteric coated tablet, film coated tablet, double coated tablet, or

multi-coated tablet.

Known carriers can be widely used in making the medical preparation in a pill form. Examples of such a carrier include excipients such as glucose, 5 lactose, starch, cacao butter, hydrogenated vegetable oil, kaoline or talc, binders such as gum arabic powder, tragacanth powder, gelatin or ethanol, and disintegrators such as laminaran or agar.

Known carriers can be widely used in making 10 the medical preparation in a suppository form. Examples of such a carrier include polyethylene glycol, cacao butter, higher alcohol, higher alcohol esters, gelatin, and semisynthetic glyceride.

In a case where the medical preparation is 15 prepared as an injection such as a liquid, emulsion or suspension, these solutions are preferably sterilized and prepared to be isotonic to blood. Known diluents can be widely used in making the medical preparation in such a liquid, emulsion or suspension form. Examples 20 of such a diluent include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, and polyoxyethylene sorbitan fatty acid esters. Moreover, in the case of using the medical preparation as an injection, a certain amount 25 of common salts, glucose or glycerin that is sufficient to prepare an isotonic solution may be added to the medical preparation. Otherwise, a common solubilizing agent, buffer, soothing agent or the like may also be

added to the medical preparation. Further, a coloring agent, preservative, perfume, flavor, sweetening agent or other pharmaceuticals may also be added thereto, if necessary.

5 The amount of the compound of the present invention contained in the medical preparation is not particularly limited, but it can be appropriately selected from a wide range. Generally, 1 to 70% by weight of the compound of the present invention is
10 preferably contained in the medical preparation.

 The method of administering the medical preparation of the present invention is not particularly limited. It is administered depending on various preparation forms, patients' age, sex, conditions of
15 disease, or other conditions. For example, where the medical preparation adopts a tablet, pill, liquid, suspension, emulsion, granule or capsule form, it is administered orally. In the case of an injection, it can be administered intravenously, singly or in
20 combination with a common auxiliary fluid such as glucose or amino acid. Moreover, if necessary, it can be singly administered intramuscularly, intradermally, subcutaneously or intraperitoneally. In the case of a suppository, it can be administered intrarectally.

25 The dose of the above medical preparation may be appropriately selected depending on usage, patients' age, sex, level of disease, or other conditions. Generally 0.01 to 100 mg, preferably 0.1 to 50 mg per

kg of body weight of the medical preparation is administered once or divided into several times per day.

Since the above dose is altered depending on various conditions, the dose smaller than the above range may be sufficient in some cases, or the dose greater than the above range may be required in other cases.

The compound of the present invention has a specific effect against *Mycobacterium tuberculosis* such as acid-fast bacteria (*Mycobacterium*, atypical acid-fast bacteria). The compound of the present invention has an excellent effect against multi-drug-resistant *Mycobacterium tuberculosis*. The compound of the present invention has an antimicrobial action against anaerobic bacteria.

The compound of the present invention does not only show the above described activities in vitro, but it also expresses the above activities in oral administration.

The compound of the present invention does not induce diarrhea, which is induced by known antimicrobial agents having a wide spectrum for common bacteria such as Gram-positive bacteria or Gram-negative bacteria. In addition, it has lesser adverse reactions than existing agents. Accordingly, it can be a medical preparation, which can be administered for a long time.

The compound of the present invention can be distributed well in the tissues of the lung, the main organ that is infected by acid-fast bacteria, and it has properties such as sustained efficacy or excellent
5 safety. Accordingly, a high therapeutic effect can be expected from the compound.

When compared with existing antitubercular agents, the compound of the present invention shows a strong bactericidal action even towards cytozoic
10 bacteria such as Mycobacterium tuberculosis present in a human macrophage. Accordingly, it enables a reduction of reoccurrence rate of tuberculosis and the realization of a short-term chemotherapy. It is therefore expected that the compound of the present
15 invention will also be used as a main preventive agent administered for a mixed infection by HIV and tuberculosis, which is considered to be a serious problem.

EXAMPLES

20 Formulation Example, Reference Examples, Examples and Test Examples will be described below.

Formulation Example 1

100 g of a compound of the invention, 40 g of Avicel (trade name, manufactured by Asahi Kasei
25 Corporation), 30 g of corn starch and 2 g of magnesium stearate were mixed and ground, and then formed into tablets with a pestle of sugarcoat R10 mm.

A film coating agent containing 10 g of TC-5

(trade name, hydroxypropyl methylcellulose, manufactured by Shin-Etsu Chemical Co., Ltd.), 3 g of polyethylene glycol-6000, 40 g of castor oil and an appropriate amount of ethanol was used to coat the
5 obtained tablets, producing a film-coated tablet having the composition described above.

Reference Example 1

Preparation of benzyl 4-(2-oxopropyl)piperazine-1-carboxylate

10 Potassium carbonate (1.27 g, 9.22 mmol), N-ethyldiisopropylamine (0.80 ml, 4.61 mmol), and chloroacetone (1.22 ml, 13.83 mmol) were added to a solution of benzyl piperazine-1-carboxylate (2.03 g, 9.22 mmol) in acetonitrile (20 ml), and the mixture was heated
15 under reflux for 2 hours. The insoluble substances were removed by filtration and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =
20 100/1) to afford benzyl 4-(2-oxopropyl)piperazine-1-carboxylate (2.24 g, yield 88%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.15 (3H, s), 2.35 - 2.50 (4H, m), 3.21 (2H, s), 3.50 - 3.62 (4H, m), 5.13 (2H, s), 7.27 - 7.42 (5H, m).

25 Reference Example 2

Preparation of tert-butyl 4-(3-oxobutyl)piperazine-1-carboxylate

A solution of tert-butyl piperazine-1-

carboxylate (6 g, 32.3 mmol) in THF (50 ml) was gradually added dropwise to a solution of methyl vinyl ketone (2.3 g, 32.9 mmol) in THF (25 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford tert-butyl 4-(3-oxobutyl) piperazine-1-carboxylate (7.2 g, yield 87%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 (9H, s), 2.17 (3H, s), 2.30 - 2.42 (4H, m), 2.53 - 2.70 (4H, m), 3.33 - 3.47 (4H, m).

Using corresponding starting materials, compounds of Reference Examples 3 to 10 were prepared in the same manner as described in Reference Example 1.

Reference Example 3

1-[4-(4-trifluoromethylphenyl) piperazin-1-yl]propan-2-one

yield 99%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.18 (3H, s), 2.63 - 2.68 (4H, m), 3.27 (2H, s), 3.30 - 3.45 (4H, m), 6.92 (2H, d, $J = 8.7$ Hz), 7.48 (2H, d, $J = 8.7$ Hz).

Reference Example 4

1-(4-phenylpiperazin-1-yl)propan-2-one

yield 95%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.19 (3H, s), 2.65 - 2.70 (4H, m), 3.27 - 3.32 (6H, m),
6.97 - 7.01 (2H, m), 7.24 - 7.31 (1H, m), 7.37 - 7.43
(2H, m).

Reference Example 5

5 1-[4-(4-chlorophenyl)piperazin-1-yl]propan-2-one
yield 99%

¹H-NMR (CDCl₃) δppm:

2.17 (3H, s), 2.63 - 2.67 (4H, m), 3.18 - 3.23 (4H, m),
3.26 (2H, s), 6.80 - 6.87 (2H, m), 7.17 - 7.23 (2H, m).

10 Reference Example 6

1-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]propan-2-one

yield 100%

¹H-NMR (CDCl₃) δppm:

15 2.18 (3H, s), 2.63 - 2.68 (4H, m), 3.20 - 3.25 (4H, m),
3.26 (2H, s), 6.85 - 6.92 (2H, m), 7.09 - 7.13 (2H, m).

Reference Example 7

1-[4-(2-pyridyl)piperazin-1-yl]propan-2-one

yield 97%

20 ¹H-NMR (CDCl₃) δppm:

2.19 (3H, s), 2.58 - 2.63 (4H, m), 3.25 (2H, s), 3.57 -
3.62 (4H, m), 6.60 - 6.66 (2H, m), 7.44 - 7.51 (1H, m),
8.17 - 8.20 (1H, m).

Reference Example 8

25 1-[4-(2-pyrimidyl)piperazin-1-yl]propan-2-one
yield 88%

¹H-NMR (CDCl₃) δppm:

2.19 (3H, s), 2.53 - 2.57 (4H, m), 3.25 (2H, s), 3.86 -

3.90 (4H, m), 6.49 (1H, t, $J = 4.8$ Hz), 8.30 (2H, d, $J = 4.8$ Hz).

Reference Example 9

tert-butyl N-methyl-[1-(2-oxopropyl)piperidin-4-yl]

5 carbamate

yield 79%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.46 (9H, s), 1.57 - 1.63 (2H, m), 1.70 - 1.91 (2H, m),
2.04 - 2.18 (2H, m), 2.14 (3H, s), 2.71 - 2.74 (1H, m),
10 2.74 (3H, s), 2.90 - 2.95 (2H, m), 3.19 (2H, s).

Reference Example 10

tert-butyl 4-(2-oxopropyl)homopiperazine-1-carboxylate

yield 58%

$^1\text{H-NMR}$ (CDCl_3) δppm :

15 1.46 (9H, s), 1.75 - 1.93 (2H, m), 2.14 (3H, s), 2.64 -
2.76 (4H, m), 3.32 (2H, s), 3.38 - 3.58 (4H, m).

Reference Example 11

Preparation of 1-(4-trifluoromethylbenzoyl)-4-hydroxypiperidine

20 4-(Trifluoromethyl)benzoyl chloride (1.5 ml, 9.89 mmol) was added to a solution of 4-hydroxypiperidine (1 g, 9.89 mmol) and triethylamine (1.7 ml, 11.9 mmol) in methylene chloride (20 ml) while cooling in an ice-bath, and the mixture was stirred at room
25 temperature for 30 minutes. The reaction mixture was washed with water, saturated sodium bicarbonate aqueous solution and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under

reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/acetone = 2/1) to afford 1-(4-trifluoromethylbenzoyl)-4-hydroxypiperidine (2.07 g, yield 77%) as a colorless crystalline powder.

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.36 - 2.07 (4H, m), 3.07 - 3.70 (3H, m), 3.91 - 4.32 (2H, m), 7.51 (2H, d, $J = 8.0$ Hz), 7.68 (2H, d, $J = 8.0$ Hz).

Using a corresponding starting material, a
10 compound of Reference Example 12 was prepared in the same manner as described in Reference Example 11.

Reference Example 12

1-(4-trifluoromethoxybenzoyl)-4-hydroxypiperidine
a colorless crystalline powder, yield 100%

15 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.34 - 2.07 (4H, m), 3.09 - 3.80 (3H, m), 3.91 - 4.32 (2H, m), 7.25 (2H, d, $J = 7.9$ Hz), 7.45 (2H, d, $J = 7.9$ Hz).

Reference Example 13

20 Preparation of 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethylphenoxy)piperidine

A mixture of 4-(4-trifluoromethylphenoxy)-piperidine (1.87 g, 7.63 mmol), 2-(2-bromoethoxy)-tetrahydropyran (1.75 g, 8.4 mmol), potassium carbonate
25 (1.16 g, 8.38 mmol), sodium iodide (1.2 g, 8.01 mmol) in DMF (30 ml) was stirred at 100°C for 1 hour. The reaction mixture was allowed to return to room temperature, poured into water and extracted with ethyl

acetate twice. The extract was washed with water twice and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel

5 column chromatography (methylene chloride/methanol = 50/1) to afford 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethylphenoxy)piperidine (1.69 g, yield 59%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

10 1.39 - 2.12 (10H, m), 2.36 - 2.53 (2H, m), 2.68 (2H, t, J = 6.1 Hz), 2.71 - 2.92 (2H, m), 3.43 - 3.63 (2H, m), 3.78 - 3.94 (2H, m), 4.31 - 4.47 (1H, m), 4.57 - 4.67 (1H, m), 6.96 (2H, d, J = 8.7 Hz), 7.52 (2H, d, J = 8.7 Hz).

15 Reference Example 14

Preparation of 2-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]ethanol

A mixture of 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethylphenoxy)piperidine
20 (1.69 g, 4.53 mmol) prepared in Reference Example 13 and pyridinium p-toluenesulfonate (114 mg, 0.45 mmol) in ethanol (50 ml) was stirred at 60 to 70°C for 6 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced
25 pressure. To the residue, 10% sodium hydroxide aqueous solution was added, and the mixture was extracted with methylene chloride. The extract was washed with brine and dried over magnesium sulfate. After filtration,

the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 2-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]ethanol (1.19 g, yield 91%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.73 - 2.10 (4H, m), 2.31 - 2.47 (2H, m), 2.58 (2H, t, J = 5.5 Hz), 2.69 - 3.00 (3H, m), 3.63 (2H, t, J = 5.5 Hz), 4.33 - 4.48 (1H, m), 6.95 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.6 Hz).

Reference Example 15

Preparation of 2-[2-(4-trifluoromethylphenoxy)ethoxy]-tetrahydropyran

A mixture of 4-hydroxybenzotrifluoride (2.08 g, 12.83 mmol), 2-(2-bromoethoxy)tetrahydropyran (3 g, 14.11 mmol), potassium carbonate (1.95 g, 14.11 mmol), and sodium iodide (2 g, 13.47 mmol) in DMF (15 ml) was stirred at 100°C for 3 hours. The reaction mixture was allowed to return to room temperature, poured into water, and extracted with ethyl acetate twice. The extract was washed with water twice and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford 2-[2-(4-trifluoromethylphenoxy)ethoxy]tetrahydropyran (2.47 g, yield 66%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.41 - 1.90 (6H, m), 3.45 - 3.66 (1H, m), 3.76 - 3.96 (2H, m), 4.02 - 4.24 (3H, m), 4.63 - 4.76 (1H, m), 6.98 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.6 Hz).

Reference Example 16

5 Preparation of 2-(4-trifluoromethylphenoxy)ethanol

Using 2-[2-(4-trifluoromethylphenoxy)ethoxy]-tetrahydropyran (2.47 g, 8.51 mmol) prepared in Reference Example 15, 2-(4-trifluoromethylphenoxy)-ethanol (1.32 g, yield 79%) as a colorless crystalline powder was prepared in the same manner as described in Reference Example 14.

¹H-NMR (CDCl₃) δppm:

3.88 - 4.14 (4H, m), 6.98 (2H, d, J = 8.6 Hz), 7.55 (2H, d, J = 8.6 Hz).

15 Reference Example 17

Preparation of 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine

Using 4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine monohydrochloride (680 mg, 2.43 mmol) and 2-(2-bromoethoxy)tetrahydropyran (610 mg, 2.92 mmol), 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine (425 mg, yield 47%) as a pale brown oil was prepared in the same manner as described in Reference Example 15.

25 ¹H-NMR (CDCl₃) δppm:

1.41 - 1.92 (6H, m), 2.45 - 2.59 (2H, m), 2.67 - 2.86 (4H, m), 3.18 - 3.31 (2H, m), 3.43 - 3.65 (2H, m), 3.80 - 4.00 (2H, m), 4.55 - 4.65 (1H, m), 5.98 - 6.10 (1H,

m), 7.15 (2H, dd, $J = 2.1$ Hz, 8.8 Hz), 7.38 (2H, dd, $J = 2.1$ Hz, 8.8 Hz).

Reference Example 18

Preparation of 2-[4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridin-1-yl]ethanol

Using 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine (425 mg, 1.14 mmol) prepared in Reference Example 17, 2-[4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridin-1-yl]ethanol (222 mg, yield 68%) as a pale brown oil was prepared in the same manner as described in Reference Example 14.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.47 - 2.59 (2H, m), 2.68 (2H, t, $J = 5.5$ Hz), 2.79 (2H, t, $J = 5.5$ Hz), 3.16 - 3.25 (2H, m), 3.70 (2H, t, $J = 5.5$ Hz), 6.00 - 6.10 (1H, m), 7.17 (2H, dd, $J = 2.1$ Hz, 6.7 Hz), 7.40 (2H, dd, $J = 2.1$ Hz, 6.7 Hz).

Reference Example 19

Preparation of 3-(4-trifluoromethylphenyl)-2-propyn-1-ol

A mixture of 4-bromobenzotrifluoride (6.5 g, 28.89 mmol), propargyl alcohol (2.35 ml, 40.45 mmol), triethylamine (5.64 ml, 40.45 mmol), triphenylphosphine (230 mg, 0.87 mmol), cuprous iodide (110 mg, 0.58 mmol), and dichlorobis (triphenylphosphine) palladium (210 mg, 0.29 mmol) in toluene (100 ml) was stirred at 100°C under a nitrogen atmosphere for 2 hours. The reaction mixture was allowed to return to room

temperature and filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 3-(4-trifluoromethylphenyl)-2-propyn-1-ol (3.47 g, yield 60%) as a pale brown oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

4.52 (2H, d, $J = 6.2$ Hz), 7.53 (2H, d, $J = 8.7$ Hz), 7.58 (2H, d, $J = 8.7$ Hz).

10 Reference Example 20

Preparation of 2-[N-methyl-(4-trifluoromethoxyphenyl)-amino]ethanol

A mixture of N-methyl-(4-trifluoromethoxyphenyl)amine (4.83 g, 24.24 mmol), 2-(2-bromoethoxy)-tetrahydropyran (6.1 g, 29.03 mmol), and potassium carbonate (3.84 g, 27.76 mmol) in DMF (20 ml) was stirred at 100°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water, and extracted with ethyl acetate twice. The extract was washed with water twice and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford 2-[N-methyl-(4-trifluoromethoxyphenyl)-amino]ethanol (3.1 g, yield 53%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.96 (3H, s), 3.46 (2H, t, $J = 5.7$ Hz), 3.81 (2H, q, J

= 5.7 Hz), 6.74 (2H, d, $J = 8.7$ Hz), 7.08 (2H, d, $J = 8.7$ Hz).

Reference Example 21

Preparation of 8-(4-trifluoromethoxyphenyl)-1,4-dioxaspiro[4.5]decane

A mixture of 1-bromo-4-(trifluoromethoxy)benzene (6.3 g, 26.14 mmol), 1,4-dioxaspiro[4.5]decane (3.35 ml, 26.14 mmol), palladium acetate (60 mg, 0.26 mmol), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (244 mg, 0.39 mmol), and sodium tert-butoxide (3.77 g, 39.23 mmol) in toluene (50 ml) was stirred at 80°C for 1 hour. The reaction mixture was allowed to return to room temperature, to which ethyl acetate (50 ml) was added, and the resulting mixture was then filtered. The filtrate was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 8-(4-trifluoromethoxyphenyl)-1,4-dioxaspiro[4.5]decane (6.54 g, yield 83%) as a pale yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.83 (4H, t, $J = 5.8$ Hz), 3.31 (4H, t, $J = 5.8$ Hz), 3.99 (4H, s), 6.90 (2H, d, $J = 8.8$ Hz), 7.09 (2H, d, $J = 8.8$ Hz).

Reference Example 22

Preparation of 1-(4-trifluoromethoxyphenyl)piperidin-4-

one

A mixture of 8-(4-trifluoromethoxyphenyl)-1,4-dioxo-8-azaspiro[4.5]decane (1.23 g, 4.06 mmol) prepared in Reference Example 21, concentrated hydrochloric acid (5 ml), water (10 ml), and ethanol (30 ml) was heated under reflux for 5 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, 10% sodium hydroxide aqueous solution was added, and the mixture was extracted with methylene chloride. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) to afford 1-(4-trifluoromethoxyphenyl)piperidin-4-one (848 mg, yield 81%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.56 (4H, t, $J = 6.2$ Hz), 3.59 (4H, t, $J = 6.2$ Hz), 6.94 (2H, d, $J = 8.5$ Hz), 7.14 (2H, d, $J = 8.5$ Hz).

Reference Example 23

Preparation of 1-(4-trifluoromethoxyphenyl)piperidin-4-ol

Sodium borohydride (324 mg, 8.56 mmol) was added to a solution of 1-(4-trifluoromethoxyphenyl)piperidin-4-one (1.11 g, 4.28 mmol) prepared in Reference Example 22 in methanol (30 ml) while cooling in an ice-bath, and the mixture was stirred for 30

minutes. To which 10% hydrochloric acid was added, and the resulting mixture was concentrated under reduced pressure. To the residue saturated sodium bicarbonate aqueous solution was added, and the mixture was
5 extracted with methylene chloride. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-
10 hexane/ethyl acetate = 3/1) to afford 1-(4-trifluoromethoxyphenyl)piperidin-4-ol (1.08 g, yield 97%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.59 - 1.76 (2H, m), 1.90 - 2.06 (2H, m), 2.82 - 2.98
15 (2H, m), 3.43 - 3.57 (2H, m), 3.75 - 3.91 (1H, m), 6.89 (2H, d, $J = 7.1$ Hz), 7.09 (2H, d, $J = 7.1$ Hz).

Compounds of Reference Examples 24 and 25 were prepared in the same manner as described in Example 23.

20 Reference Example 24

1-(4-trifluoromethylphenyl)piperidin-4-ol
a white powder, yield 76%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.53 - 1.71 (2H, m), 1.89 - 2.04 (2H, m), 2.91 - 3.11
25 (2H, m), 3.56 - 3.71 (2H, m), 3.80 - 4.00 (1H, m), 6.93 (2H, d, $J = 8.7$ Hz), 7.46 (2H, d, $J = 8.7$ Hz).

Reference Example 25

1-(4-methoxyphenyl)piperidin-4-ol

a white powder, yield 5%

^1H -NMR (CDCl_3) δ ppm:

1.64 - 1.79 (2H, m), 1.92 - 2.08 (2H, m), 2.74 - 2.88
(2H, m), 3.32 - 3.47 (2H, m), 3.70 - 3.85 (4H, m), 6.84
5 (2H, dd, $J = 2.4$ Hz, 6.8 Hz), 6.93 (2H, dd, $J = 2.4$ Hz,
6.8 Hz).

Reference Example 26

Preparation of 1-(4-chlorophenyl)piperidin-4-ol

A mixture of 8-(4-chlorophenyl)-1,4-dioxo-8-
10 azaspiro[4.5]decane (2.6 g, 10.25 mmol), concentrated
hydrochloric acid (12 ml), water (10 ml), and ethanol
(50 ml) was heated under reflux for 5 hours. The
reaction mixture was allowed to return to room
temperature and concentrated under reduced pressure.
15 To the residue 10% sodium hydroxide aqueous solution
was added, and the mixture was extracted with methylene
chloride. The extract was washed with water and brine,
and dried over magnesium sulfate. After filtration,
the filtrate was concentrated under reduced pressure.
20 The residue was dissolved in methanol (50 ml), to which
sodium borohydride (388 mg, 10.25 mmol) was added while
cooling in an ice-bath, and the mixture was stirred for
30 minutes. To the reaction mixture, 10% hydrochloric
acid was added, and the mixture was concentrated under
25 reduced pressure. Saturated sodium bicarbonate aqueous
solution was added to the residue, and the mixture was
extracted with methylene chloride. The extract was
washed with water and brine, and was dried over

magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) to afford 1-(4-chlorophenyl)piperidin-4-ol (1.73 g, yield 80%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.55 - 1.74 (2H, m), 1.89 - 2.08 (2H, m), 2.79 - 3.00 (2H, m), 3.43 - 3.57 (2H, m), 3.75 - 3.92 (1H, br),
 10 6.89 (2H, d, J = 7.1 Hz), 7.09 (2H, d, J = 7.1 Hz).

Using a corresponding starting material, a compound of Reference Example 27 was prepared in the same manner as described in Reference Example 26.

Reference Example 27

15 1-(4-fluorophenyl)piperidin-4-ol
 a white powder, yield 66%

¹H-NMR (CDCl₃) δppm:

1.57 - 1.79 (2H, m), 1.92 - 2.08 (2H, m), 2.75 - 2.92 (2H, m), 3.36 - 3.50 (2H, m), 3.74 - 3.89 (1H, m), 6.77
 20 - 7.00 (4H, m).

Reference Example 28

Preparation of 4-[4-(tert-butyldimethylsiloxy)piperidin-1-yl]benzonitrile

A mixture of 4-bromobenzonitrile (2.76 g, 15.16 mmol), 4-(tert-butyldimethylsiloxy)piperidine (2.9 g, 13.79 mmol), palladium acetate (62 mg, 0.28 mmol), (S)-(-)-2,2'-bis (diphenylphosphino)-1,1'-binaphthyl (BINAP) (258 mg, 0.41 mmol), and sodium

tert-butoxide (1.99 g, 20.68 mmol) in toluene (60 ml) was stirred at 80°C for 1 hour. The reaction mixture was allowed to return to room temperature, to which ethyl acetate (60 ml) was added, and the mixture was
5 filtered. The filtration was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/methylene chloride =
10 1/1) to afford 4-[4-(tert-butyltrimethylsiloxy)piperidin-1-yl]benzonitrile (2.8 g, yield 66%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

0.90 (9H, s), 1.50 - 1.69 (8H, m), 1.73 - 1.90 (2H, m), 3.18 - 3.31 (2H, m), 3.50 - 3.65 (2H, m), 3.90 -
15 4.04 (1H, m), 6.85 (2H, d, J = 7.0 Hz), 7.47 (2H, d, J = 7.0 Hz).

Reference Example 29

Preparation of 4-(4-hydroxypiperidin-1-yl)benzonitrile
20 Tetra-n-butylammonium fluoride (1M) THF solution (10.6 ml, 10.2 mmol) was added to a mixture of 4-[4-(tert-butyltrimethylsiloxy)piperidin-1-yl]benzonitrile (2.8 g, 8.85 mmol) prepared in Reference Example 28 in THF (30 ml) while cooling in an
25 ice-bath, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with

ethyl acetate twice. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel

5 column chromatography (n-hexane/ethyl acetate = 1/2) to afford 4-(4-hydroxypiperidin-1-yl)benzonitrile (1.52 g, yield 85%) as a colorless crystalline powder..

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.50 - 1.73 (2H, m), 1.90 - 2.04 (2H, m), 3.00 - 3.20
10 (2H, m), 3.59 - 3.76 (2H, m), 3.84 - 4.04 (1H, m), 6.86
(2H, dd, $J = 2.0$ Hz, 7.1 Hz), 7.48 (2H, dd, $J = 2.0$ Hz, 7.1 Hz).

Reference Example 30

Preparation of ethyl 1-(4-trifluoromethylphenyl)-
15 piperidine-4-carboxylate

Using 4-bromobenzotrifluoride (3.15 g, 13.99 mmol) and ethyl isonipecotate (2.2 g, 13.99 mmol), ethyl 1-(4-trifluoromethylphenyl)piperidine-4-carboxylate (3.18 g, yield 74%) as a pale brown
20 crystalline powder was prepared in the same manner as described in Reference Example 21.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.27 (3H, t, $J = 7.2$ Hz), 1.71 - 2.10 (4H, m), 2.41 -
2.55 (1H, m), 2.82 - 2.98 (2H, m), 3.65 - 3.80 (2H, m),
25 4.16 (2H, q, $J = 7.2$ Hz), 6.92 (2H, d, $J = 6.9$ Hz),
7.63 (2H, d, $J = 6.9$ Hz).

Reference Example 31

Preparation of [1-(4-trifluoromethylphenyl)piperidin-4-

yl]methanol

Lithium aluminum hydride (1.58 g, 41.64 mmol) was suspended in THF (30 ml), to which a solution of ethyl 1-(4-trifluoromethylphenyl)piperidine-4-carboxylate prepared in Reference Example 30 (3.18 g, 10.41 mmol) in THF (10 ml) was added dropwise therein while cooling in an ice-bath under a nitrogen atmosphere. The mixture was stirred for 30 minutes. Water and 10% sodium hydroxide aqueous solution were added to the reaction mixture, which was filtered through Celite. The filtrate was extracted with ethyl acetate twice. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford [1-(4-trifluoromethylphenyl)-piperidin-4-yl]methanol (2.64 g, yield 98%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.31 - 1.47 (2H, m), 1.61 - 1.90 (3H, m), 2.74 - 2.90 (2H, m), 3.45 - 3.61 (2H, m), 3.83 (2H, d, $J = 12.6$ Hz), 6.92 (2H, d, $J = 8.8$ Hz), 7.46 (2H, d, $J = 8.8$ Hz).

Reference Example 32

Preparation of 1-(4-trifluoromethoxybenzyl)piperidin-4-ol

Sodium triacetoxymethylborohydride (1.67 g, 7.89 mmol) was added to a solution of 4-(trifluoromethoxy)benzaldehyde (1 g, 5.26 mmol) and 4-hydroxy piperidine

(798 mg, 7.89 mmol) in acetonitrile (2 ml) while cooling in an ice-bath, and the mixture was stirred for 30 minutes, and then at room temperature overnight.

The reaction mixture was poured into 7.5% sodium

5 bicarbonate aqueous solution and extracted with ethyl acetate twice. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel

10 column chromatography (methylene chloride/methanol = 10/1) to afford 1-(4-trifluoromethoxybenzyl)piperidin-4-ol (1.21 g, yield 84%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.50 - 1.74 (2H, m), 1.80 - 1.98 (2H, m), 2.08 - 2.24
15 (2H, m), 2.63 - 2.84 (2H, m), 3.49 (2H, s), 3.61 - 3.80 (1H, m), 7.15 (2H, d, J = 8.5 Hz), 7.34 (2H, d, J = 8.5 Hz).

Compounds of Reference Examples 33 and 34 were prepared in the same manner as described in

20 Reference Example 32.

Reference Example 33

1-(4-chlorobenzyl) piperidin-4-ol

a white powder, yield 87%

¹H-NMR (CDCl₃) δppm:

25 1.48 - 1.63 (2H, m), 1.76 - 1.91 (2H, m), 2.04 - 2.20 (2H, m), 2.61 - 2.76 (2H, m), 3.45 (2H, s), 3.57 - 3.72 (1H, m), 7.24 (2H, d, J = 8.8 Hz), 7.28 (2H, d, J = 8.8 Hz).

Reference Example 34

1-(4-trifluoromethylbenzyl) piperidin-4-ol

a white powder, yield 83%

¹H-NMR (CDCl₃) δppm:

- 5 1.43 - 1.67 (2H, m), 1.80 - 1.94 (2H, m), 2.06 - 2.24
(2H, m), 2.63 - 2.78 (2H, m), 3.67 (2H, s), 3.61 - 3.72
(1H, m), 7.44 (2H, d, J = 8.0 Hz), 7.57 (2H, d, J = 8.0
Hz).

Reference Example 35

- 10 Preparation of tert-butyl(4-benzylpiperazin-1-
yl)carbamate

4-Benzylpiperazin-1-yl-amine (36.03 g, 188
mmol) was dissolved in methanol (260 ml) and the
solution was cooled in an ice-bath, to which a solution
15 of di-tert-butyl dicarbonate (61.66 g, 283 mmol) in
methanol (100 ml) was added dropwise over 20 minutes.
The mixture was allowed to return to room temperature
and stirred overnight. The reaction mixture was
concentrated under reduced pressure, and the residue
20 was purified by silica gel column chromatography (n-
hexane/acetone = 3/1). Isopropyl ether (IPE) (60 ml)
and n-hexane (20 ml) were added to thus obtained solid,
and the mixture was stirred and then filtered to afford
primary crystals. The filtrate was concentrated under
25 reduced pressure, isopropyl ether (10 ml) and n-hexane
(10 ml) were added to the residue, and the mixture was
stirred and then filtered to afford secondary crystals.
These crystals were combined and dried under reduced

pressure to afford tert-butyl(4-benzylpiperazin-1-yl)carbamate (42.22 g, yield 77%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

5 1.45 (9H, s), 2.55 - 2.58 (4H, m), 2.80 (4H, br), 3.51 (2H, s), 5.35 (1H, br), 7.24 - 7.31 (5H, m).

Reference Example 36

Preparation of tert-butyl piperazin-1-yl-carbamate

Tert-butyl(4-benzylpiperazin-1-yl)carbamate

10 (42.22 g, 145 mmol) prepared in Reference Example 35 was dissolved in ethanol (300 ml). To which 20% palladium hydroxide/carbon (6.0 g) was added, and the mixture was stirred at room temperature under an atmospheric pressure of hydrogen for 20 minutes, and
15 then at 50°C for 30 minutes. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Thus obtained solid was washed with IPE, collected by filtration, and dried under reduced pressure to afford tert-butyl piperazin-1-yl-carbamate
20 (28.9 g, yield 99%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 2.74 - 2.77 (4H, m), 2.95 - 2.99 (4H, m), 5.45 (1H, br).

Reference Example 37

25 Preparation of tert-butyl 4-(4-trifluoromethyl phenoxy)piperidine-1-carboxylate

Tert-butyl 4-hydroxypiperidine-1-carboxylate

(2.22 g, 10.0 mmol), 4-hydroxybenzotrifluoride (1.21 g,

7.45 mmol), tri-n-butylphosphine (2.26 g, 11.2 mmol) and 1,1'-(azodicarbonyl) dipiperidine (2.82 g, 11.2 mmol) were dissolved in benzene (20 ml), and the mixture was stirred at room temperature for 2 days. To
5 which water was added, and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate and thereafter filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 5/1) to afford tert-butyl 4-(4-trifluoromethylphenoxy)piperidine-1-carboxylate (1.13 g, yield 44%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.48 (9H, s), 1.65 - 1.82 (2H, m), 1.87 - 1.97 (2H, m),
15 3.34 - 3.44 (2H, m), 3.63 - 3.74 (2H, m), 4.47 - 4.58 (1H, m), 6.89 - 6.97 (2H, m), 7.47 - 7.55 (2H, m).

Reference Example 38

Preparation of 4-(4-trifluoromethylphenoxy)piperidine

Tert-butyl 4-(4-trifluoromethylphenoxy)-
20 piperidine-1-carboxylate (1.13 g, 3.27 mmol) prepared in Reference Example 37 was dissolved in methylene chloride (10 ml). To which trifluoroacetic acid (10 ml) was added dropwise and the mixture was stirred at room temperature for 5 hours. After the reaction
25 mixture was concentrated under reduced pressure, the residue was again dissolved in methylene chloride. The solution was neutralized with a sodium hydroxide aqueous solution, and the mixture was extracted with

methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 4-(4-trifluoromethylphenoxy)piperidine (727 mg, 5 yield 91%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.63 - 1.75 (2H, m), 1.97 - 2.06 (2H, m), 2.69 - 2.80 (2H, m), 3.10 - 3.20 (2H, m), 4.38 - 4.49 (1H, m), 6.94 - 6.98 (2H, m), 7.50 - 7.55 (2H, m).

10 Using corresponding starting materials, compounds of Reference Examples 39 to 43 were prepared in the same manner as described in Reference Example 38.

Reference Example 39

15 4-(4-fluorophenoxy)piperidine
a white powder, yield 76%

¹H-NMR (CDCl₃) δppm:

1.61 - 1.74 (2H, m), 1.96 - 2.06 (2H, m), 2.50 (1H, bs), 2.70 - 2.80 (2H, m), 3.11 - 3.20 (2H, m), 4.23 - 20 4.33 (1H, m), 6.80 - 6.89 (2H, m), 6.91 - 7.00 (2H, m).

Reference Example 40

4-(3-trifluoromethylphenoxy)piperidine
a white powder, yield 48%

¹H-NMR (CDCl₃) δppm:

25 1.62 - 1.76 (2H, m), 1.80 (1H, bs), 1.97 - 2.08 (2H, m), 2.71 - 2.81 (2H, m), 3.11 - 3.20 (2H, m), 4.37 - 4.47 (1H, m), 7.05 - 7.20 (3H, m), 7.34 - 7.41 (1H, m).

Reference Example 41

4-(4-trifluoromethoxyphenoxy)piperidine

a white powder, yield 88%

¹H-NMR (CDCl₃) δppm:

1.59 - 1.73 (3H, m), 1.97 - 2.04 (2H, m), 2.68 - 2.78
5 (2H, m), 3.10 - 3.19 (2H, m), 4.29 - 4.36 (1H, m), 6.85
- 6.92 (2H, m), 7.10 - 7.14 (2H, m).

Reference Example 42

4-(4-cyanophenoxy)piperidine

a white powder, yield 83%

10 ¹H-NMR (CDCl₃) δppm:

1.63 - 1.77 (3H, m), 1.98 - 2.08 (2H, m), 2.72 - 2.82
(2H, m), 3.12 - 3.21 (2H, m), 4.42 - 4.51 (1H, m), 6.92
- 6.98 (2H, m), 7.55 - 7.61 (2H, m).

Reference Example 43

15 4-(4-chlorophenoxy)piperidine

a white powder, yield 62%

¹H-NMR (CDCl₃) δppm:

1.50 (1H, bs), 1.56 - 1.71 (2H, m), 1.94 - 2.04 (2H,
m), 2.66 - 2.76 (2H, m), 3.08 - 3.18 (2H, m), 4.25 -
20 4.35 (1H, m), 6.80 - 6.86 (2H, m), 7.18 - 7.25 (2H, m).

Reference Example 44

Preparation of 1-ethyl-5-(3-methyl-3-butenyl)-1H-
tetrazole

n-Butyl lithium (1.53 M) hexane solution (6.5
25 ml, 9.98 mmol) was added dropwise to a solution of 1-
ethyl-5-methyl-1H-tetrazole (0.80 g, 7.13 mmol) in THF
(15 ml) while stirring at -70°C, and the mixture was
further stirred for 1.5 hours. A solution of 3-chloro-

2-methyl-1-propene (0.77 ml, 7.84 mmol) in THF (5 ml) was added to the mixture, and the resulting mixture was stirred for 2 hours. Water was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and then concentrated under reduced pressure to afford 1-ethyl-5-(3-methyl-3-butenyl)-1H-tetrazole (0.95 g, yield 80%) as a brown oil.

¹H-NMR (CDCl₃) δppm:

1.56 (3H, t, J = 7.3 Hz), 1.80 (3H, s), 2.44 - 2.67 (2H, m), 2.90 - 3.06 (2H, m), 4.32 (2H, q, J = 7.3 Hz), 4.65 - 4.77 (1H, m), 4.77 - 4.87 (1H, m).

Using corresponding starting materials, compounds of Reference Examples 45 and 46 were prepared in the same manner as described in Reference Example 44.

Reference Example 45

1-phenyl-5-(3-methyl-3-butenyl)-1H-tetrazole
a white powder, yield 45%

¹H-NMR (CDCl₃) δppm:

1.67 (3H, s), 2.49 (2H, t, J = 8.1 Hz), 3.04 (2H, t, J = 8.1 Hz), 4.58 - 4.65 (1H, m), 4.71 - 4.77 (1H, m), 7.43 - 7.47 (2H, m), 7.59 - 7.62 (3H, m).

Reference Example 46

1-(4-chlorophenyl)-5-(3-methyl-3-butenyl)-1H-tetrazole
a white powder, yield 55%

¹H-NMR (CDCl₃) δppm:

1.68 (3H, s), 2.50 (2H, t, J = 8.1 Hz), 3.03 (2H, t, J

= 8.1 Hz), 4.58 - 4.63 (1H, m), 4.71 - 4.77 (1H, m),
7.38 - 7.44 (2H, m), 7.56 - 7.62 (2H, m).

Reference Example 47

Preparation of 3-(4-methyl-4-pentenyl)-3H-benzoxazol-2-
5 one

Potassium tert-butoxide (3.5 g, 31.2 mmol)
was gradually added to a mixture of methyltriphenyl-
phosphonium bromide (11 g, 30.8 mmol) in THF (100 ml)
while cooling in an ice-bath, and the mixture was
10 stirred for 20 minutes. To which a solution of 3-(4-
oxopentyl)-3H-benzoxazol-2-one (5.6 g, 25.6 mmol) in
THF (10 ml) was gradually added dropwise. The
resulting mixture was stirred at room temperature for 2
hours. The reaction mixture was poured into ice water,
15 and extracted with ethyl acetate twice. The extract
was washed with water and brine, and dried over sodium
sulfate. After filtration, the filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (n-
20 hexane/ethyl acetate = 3/1) to afford 3-(4-methyl-4-
pentenyl)-3H-benzoxazol-2-one (3.4 g, yield 61%) as a
colorless oil.

¹H-NMR (CDCl₃) δppm:

1.73 (3H, s), 1.84 - 2.16 (4H, m), 3.83 (2H, t, J = 7.3
25 Hz), 4.75 (2H, d, J = 12.7 Hz), 6.97 (1H, d, J = 8.2
Hz), 7.02 - 7.28 (3H, m).

Reference Example 48

Preparation of 3-(5-methyl-5-hexenyl)-3H-benzoxazol-2-

one

Using 3-(5-oxohexyl)-3H-benzoxazol-2-one (1.4 g, 6 mmol), 3-(5-methyl-5-hexenyl)-3H-benzoxazol-2-one (1.1 g, yield 79%) as a colorless oil was prepared in the same manner as described in Reference Example 47.

¹H-NMR (CDCl₃) δppm:

1.42 - 1.60 (2H, m), 1.65 - 1.83 (5H, m), 2.00 - 2.16 (2H, m), 3.84 (2H, t, J = 6.9 Hz), 4.69 (2H, d, J = 11.7 Hz), 6.97 (1H, d, J = 7.9 Hz), 7.02 - 7.23 (3H, m).

Reference Example 49

Preparation of 5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

Triethylamine (3.52 ml, 25.28 mmol) and 1,1'-carbonyldiimidazole (4.84 g, 29.87 mmol) were added to a solution of 4-trifluoromethoxybenzoic hydrazide (5.06 g, 22.98 mmol) in THF (150 ml) while cooling in an ice-bath and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, to which water was added. The mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate and then concentrated under reduced pressure to afford 5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (5.34 g, yield 94%) as a colorless crystalline powder.

¹H-NMR (DMSO-d₆) δppm:

7.01 (1H, s), 7.47 - 7.59 (2H, m), 7.86 - 7.98 (2H, m).

Using corresponding starting materials,

compounds of Reference Examples 50 to 61 were prepared in the same manner as described in Reference Example 49.

Reference Example 50

- 5 5-(4-trifluoromethylphenyl)-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 97%

¹H-NMR (DMSO-d₆) δppm:

7.90 (2H, d, J = 8.5 Hz), 7.99 (2H, d, J = 8.5 Hz).

Reference Example 51

- 10 5-(4-biphenyl)-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 97%

¹H-NMR (DMSO-d₆) δppm:

7.35 - 7.52 (3H, m), 7.68 - 7.73 (2H, m), 7.76 - 7.87
(4H, m).

- 15 Reference Example 52

5-phenyl-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 92%

¹H-NMR (CDCl₃) δppm:

7.40 - 7.58 (3H, m), 7.77 - 7.91 (2H, m).

- 20 Reference Example 53

5-(4-chlorophenyl)-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 80%

¹H-NMR (DMSO-d₆) δppm:

- 7.61 (2H, dd, J = 1.9 Hz, 6.6 Hz), 7.80 (2H, dd, J =
25 1.9 Hz, 6.6 Hz).

Reference Example 54

5-(4-fluorophenyl)-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 74%

¹H-NMR (DMSO-d₆) δppm:

7.30 - 7.49 (2H, m), 7.78 - 7.92 (2H, m).

Reference Example 55

5-(4-bromophenyl)-3H-[1,3,4]oxadiazol-2-one

5 a white powder, yield 87%

¹H-NMR (DMSO-d₆) δppm:

7.65 - 7.78 (4H, m).

Reference Example 56

5-(4-chlorobenzyl)-3H-[1,3,4]oxadiazol-2-one

10 a white powder, yield 83%

¹H-NMR (DMSO-d₆) δppm:

3.94 (2H, s), 7.31 (2H, dd, J = 2.1 Hz, 6.4 Hz), 7.41
(2H, dd, J = 2.1 Hz, 6.4 Hz).

Reference Example 57

15 5-[2-(4-chlorophenyl) ethyl]-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 78%

¹H-NMR (DMSO-d₆) δppm:

2.76 - 3.00 (4H, m), 7.27 (2H, d, J = 8.5 Hz), 7.35
(2H, d, J = 8.5 Hz), 12.03 (1H, s).

20 Reference Example 58

5-(4-chlorostyryl)-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 88%

¹H-NMR (DMSO-d₆) δppm:

6.99 (1H, d, J = 16.5 Hz), 7.32 (1H, d, J = 16.5 Hz),
25 7.47 (2H, d, J = 8.6 Hz), 7.75 (2H, d, J = 8.6 Hz),
12.06 (1H, s).

Reference Example 59

5-(4-chlorophenoxymethyl)-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 68%

¹H-NMR (DMSO-d₆) δppm:

5.07 (2H, s), 7.07 (2H, d, J = 6.8 Hz), 7.37 (2H, d, J = 6.8 Hz), 12.41 (1H, br).

5 Reference Example 60

5-(4-pyridyl)-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 40%

¹H-NMR (DMSO-d₆) δppm:

7.72 (2H, dd, J = 1.6 Hz, 4.6 Hz), 8.76 (2H, dd, J = 1.6 Hz, 4.6 Hz), 12.90 (1H, s).

 Reference Example 61

5-(2-pyrimidyl)-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 70%

¹H-NMR (DMSO-d₆) δppm:

15 8.68 - 8.86 (2H, m), 9.12 (1H, d, J = 1.4 Hz), 12.97 (1H, s).

 Reference Example 62

Preparation of tert-butyl(S)-2-(4-trifluoromethoxyphenoxy)methylpyrrolidine-1-carboxylate

20 A mixture of 4-(trifluoromethoxy)phenol (2.1 g, 11.8 mmol), tert-butyl (S)-2-hydroxymethylpyrrolidine-1-carboxylate (2 g, 9.8 mmol), diethyl azodicarboxylate (2.3 ml, 14.7 mmol), and triphenylphosphine (3.86 g, 14.7 mmol) in THF (30 ml) was heated
25 under reflux for 1 hour. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl

acetate = 10/1) to afford tert-butyl(S)-2-(4-trifluoromethoxyphenoxymethyl)pyrrolidine-1-carboxylate (2.96 g, yield 65%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

- 5 1.48 (9H, s), 1.78 - 2.10 (4H, m), 3.27 - 3.49 (2H, m),
3.73 - 3.98 (1H, m), 4.04 - 4.20 (2H, m), 6.90 (2H, dd,
J = 2.2 Hz, 7.0 Hz), 7.12 (2H, dd, J = 2.2 Hz, 7.0 Hz).

Reference Example 63

Preparation of (S)-2-(4-trifluoromethoxyphenoxymethyl)-
10 pyrrolidine

- A mixture of tert-butyl(S)-2-(4-trifluoro-
methoxyphenoxymethyl)pyrrolidine-1-carboxylate (2.31 g,
6.39 mmol) prepared in Reference Example 62,
trifluoroacetic acid (20 ml), and methylene chloride
15 (20 ml) was stirred at room temperature for 4 hours.
The reaction mixture was concentrated under reduced
pressure. The residue was neutralized with 10% sodium
hydroxide aqueous solution and the mixture was
extracted with methylene chloride, and the extract was
20 dried over magnesium sulfate. After filtration, the
filtrate was concentrated under reduced pressure to
afford (S)-2-(4-trifluoromethoxyphenoxymethyl)-
pyrrolidine (1.65 g, yield 99%) as a pale brown oil.

¹H-NMR (CDCl₃) δppm:

- 25 1.45 - 1.63 (1H, m), 1.65 - 2.04 (3H, m), 2.70 (1H,
bs), 2.88 - 3.08 (2H, m), 3.43 - 3.59 (1H, m), 3.78 -
3.96 (2H, m), 6.88 (2H, dd, J = 2.3 Hz, 8.4 Hz), 7.11
(2H, dd, J = 2.3 Hz, 8.4 Hz).

Reference Example 64

Preparation of tert-butyl 3-oxo-4-(4-trifluoromethylbenzyl)piperazine-1-carboxylate

Sodium hydride (840 mg, 24.5 mmol) was
5 gradually added to a solution of tert-butyl 3-oxopiperazine-1-carboxylate (4.1 g, 20.4 mmol) in DMF (30 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 30 minutes. A solution of 4-trifluoromethylbenzyl chloride (5 g, 20.9
10 mmol) in DMF (5 ml) was added dropwise to the mixture while cooling in an ice-bath, which was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water, and extracted with ethyl acetate twice. The extract was washed with water twice and
15 brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride) to afford tert-butyl 3-oxo-4-(4-trifluoromethylbenzyl)piperazine-
20 1-carboxylate (6.7 g, yield 91%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.47 (9H, s), 3.27 (2H, t, $J = 5.7$ Hz), 3.62 (2H, t, $J = 5.7$ Hz), 4.18 (2H, s), 4.67 (2H, s), 7.39 (2H, d, $J =$
25 8.1 Hz), 7.61 (2H, d, $J = 8.1$ Hz).

Reference Example 65

Preparation of 1-(4-trifluoromethylbenzyl)piperazin-2-one

Using tert-butyl 3-oxo-4-(4-trifluoromethylbenzyl)piperazine-1-carboxylate (6.7 g, 18.7 mmol) prepared in Reference Example 64, 1-(4-trifluoromethylbenzyl)piperazin-2-one (4.5 g, yield
5 93%) as a pale yellow powder was prepared in the same manner as described in Reference Example 63.

¹H-NMR (CDCl₃) δppm:

3.06 (2H, t, J = 5.2 Hz), 3.24 (2H, t, J = 5.2 Hz),
3.62 (2H, s), 4.60 (2H, s), 7.39 (2H, d, J = 8.1 Hz),
10 7.59 (2H, d, J = 8.1 Hz).

Reference Example 66

Preparation of 4'-trifluoromethoxybiphenyl-4-carbaldehyde

A mixture of 1-bromo-4-(trifluoromethoxy)-
15 benzene (1.53 g, 6.35 mmol), 4-formylbenzeneboronic acid (1 g, 6.67 mmol), tetrakis(triphenylphosphine)-palladium (147 mg, 0.13 mmol), and potassium phosphate (2.02 g, 9.53 mmol) in DMF (10 ml) was stirred at 100°C for 5 hours. The reaction mixture was poured into
20 water, and extracted with ethyl acetate, and the extract was washed with water three times and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column
25 chromatography (n-hexane/methylene chloride = 3/1) to afford 4'-trifluoromethoxybiphenyl-4-carbaldehyde (1.56 g, yield 92%) as a white powder.

¹H-NMR (CDCl₃) δppm:

7.33 (2H, d, $J = 8.8$ Hz), 7.60 - 7.80 (4H, m), 7.97 (2H, d, $J = 8.2$ Hz), 10.07 (1H, s).

Compounds of Reference Examples 67 to 73 were prepared from corresponding iodobenzene or bromobenzene
5 compounds and formylbenzeneboronic acids in the same manner as described in Reference Example 66.

Reference Example 67

4'-trifluoromethylbiphenyl-4-carbaldehyde

a colorless crystalline powder, yield 27%

10 $^1\text{H-NMR}$ (CDCl_3) δppm :

7.68 - 7.81 (6H, m), 7.99 (2H, dd, $J = 1.7$ Hz, 6.5 Hz), 10.09 (1H, s).

Reference Example 68

4'-trifluoromethylbiphenyl-3-carbaldehyde

15 a yellow oil, yield 83%

$^1\text{H-NMR}$ (CDCl_3) δppm :

7.33 (2H, d, $J = 8.8$ Hz), 7.60 - 7.80 (4H, m), 7.97 (2H, d, $J = 8.2$ Hz), 10.07 (1H, s).

Reference Example 69

20 4'-dimethylaminobiphenyl-4-carbaldehyde

a yellow powder, yield 46%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.03 (6H, s), 6.81 (2H, dd, $J = 2.1$ Hz, 6.8 Hz), 7.58 (2H, dd, $J = 2.1$ Hz, 6.8 Hz), 7.71 (2H, dd, $J = 1.8$ Hz, 6.6 Hz), 7.90 (2H, dd, $J = 1.8$ Hz, 6.6 Hz), 10.00 (1H, s).

Reference Example 70

4'-chlorobiphenyl-4-carbaldehyde

a pale yellow crystalline powder, yield 47%

¹H-NMR (CDCl₃) δppm:

7.45 (2H, d, J = 8.6 Hz), 7.57 (2H, d, J = 8.6 Hz),
7.73 (2H, d, J = 8.4 Hz), 7.96 (2H, d, J = 8.4 Hz),
5 10.06 (1H, s).

Reference Example 71

2'-chlorobiphenyl-4-carbaldehyde

A colorless crystalline powder, yield 46%

¹H-NMR (CDCl₃) δppm:

10 7.30 - 7.40 (3H, m), 7.38 - 7.58 (1H, m), 7.63 (2H, d,
J = 8.1 Hz), 7.96 (2H, d, J = 8.1 Hz), 10.08 (1H, s).

Reference Example 72

3',4'-dichlorobiphenyl-4-carbaldehyde

A colorless crystalline powder, yield 24%

15 ¹H-NMR (CDCl₃) δppm:

7.46 (1H, dd, J = 2.1 Hz, 8.4 Hz), 7.56 (1H, d, J = 8.4
Hz), 7.70 - 7.80 (3H, m), 7.97 (2H, dd, J = 1.8 Hz, 6.6
Hz), 10.07 (1H, s).

Reference Example 73

20 4'-methoxybiphenyl-4-carbaldehyde

A colorless crystalline powder, yield 45%

¹H-NMR (CDCl₃) δppm:

3.87 (3H, s), 7.01 (2H, d, J = 6.8 Hz), 7.59 (2H, d, J
= 6.8 Hz), 7.72 (2H, d, J = 8.3 Hz), 7.93 (2H, d, J =
25 8.3 Hz), 10.04 (1H, s).

Reference Example 74

Preparation of 4-(pyridin-3-yl)benzaldehyde

A mixture of 4-bromobenzaldehyde (2 g, 10.8

mmol), diethyl(3-pyridyl)borane (1.75 g, 11.9 mmol), tetrakis(triphenylphosphine)palladium (375 mg, 0.32 mmol), and 2N sodium carbonate aqueous solution (10.8 ml, 21.6 mmol) in toluene (40 ml) was heated under
5 reflux under a nitrogen atmosphere overnight. The reaction mixture was allowed to return to room temperature and diluted with ethyl acetate. The mixture was washed with water and brine, and dried over sodium sulfate. After filtration, the filtrate was
10 concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford 4-(pyridin-3-yl)benzaldehyde (1.43 g, yield 72%) as a pale yellow crystalline powder.

15 ¹H-NMR (CDCl₃) δppm:
7.33 - 7.50 (1H, m), 7.76 (2H, dd, J = 1.8 Hz, 6.6 Hz),
7.89 - 8.06 (3H, m), 8.56 - 8.69 (1H, m), 8.90 (1H, dd, J = 0.7 Hz, 1.7 Hz), 10.09 (1H, s).

Reference Example 75

20 Preparation of 4-(imidazol-1-yl)benzaldehyde

A mixture of 4-fluorobenzaldehyde (4.96 g, 40 mmol), imidazole (2.86 g, 42 mmol), and potassium carbonate (6.08 g, 44 mmol) in DMSO (40 ml) was stirred at 110°C overnight. The reaction mixture was allowed to
25 return to room temperature, and poured into ice water (100 ml). The resulting precipitates were collected by filtration and washed with water and then with ethyl acetate to afford 4-(imidazol-1-yl)benzaldehyde (2.33

g, yield 34%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

7.20 - 7.30 (1H, m), 7.38 (1H, dd, J = 1.3 Hz, 1.4 Hz),
7.58 (2H, dd, J = 1.8 Hz, 6.8 Hz), 7.98 - 8.10 (3H, m),
5 10.05 (1H, s).

Using a corresponding starting material, a compound of Reference Example 76 was prepared in the same manner as described in Reference Example 75.

Reference Example 76

10 4-(piperidin-1-yl)benzaldehyde

a yellow crystalline powder, yield 46%

¹H-NMR (CDCl₃) δppm:

1.58 - 1.75 (6H, m), 3.33 - 3.50 (4H, m), 6.89 (2H, dd,
J = 1.9 Hz, 7.0 Hz), 7.73 (2H, dd, J = 1.9 Hz, 7.0 Hz),
15 9.75 (1H, s).

Reference Example 77

Preparation of tert-butyl 4-(4-trifluoromethylphenyl)-
piperazine-1-carboxylate

A mixture of 4-bromobenzotrifluoride (3.0 g,
20 13.3 mmol), tert-butyl piperazine-1-carboxylate (2.9 g,
15.3 mmol), bis (dibenzylideneacetone) palladium (306
mg, 0.53 mmol), tri-o-tolylphosphine (162 mg, 0.53
mmol), and sodium tert-butoxide (2.2 g, 22.7 mmol) in
toluene (60 ml) was refluxed under a nitrogen
25 atmosphere for 4 hours. Ethyl acetate and water were
added to the reaction mixture, which was stirred for a
while, and the insoluble substances were removed by
filtration through Celite, and the filtrate was then

extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel
5 column chromatography (n-hexane/methylene chloride = 2/1) to afford tert-butyl 4-(4-trifluoromethylphenyl)-piperazine-1-carboxylate (3.8 g, yield 87%) as a white powder.

¹H-NMR (CDCl₃) δppm:

10 1.49 (9H, s), 3.21 - 3.26 (4H, m), 3.56 - 3.61 (4H, m),
6.90 - 6.93 (2H, m), 7.47 - 7.51 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 78 to 84 were prepared in the same manner as described in Reference Example
15 77.

Reference Example 78

tert-butyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate

a white powder, yield 95%

20 ¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 3.09 - 3.13 (4H, m), 3.55 - 3.60 (4H, m),
6.87 - 6.91 (2H, m), 7.10 - 7.14 (2H, m).

Reference Example 79

tert-butyl 4-(4-biphenylyl)piperazine-1-carboxylate

25 a white powder, yield 95%

¹H-NMR (CDCl₃) δppm:

1.49 (9H, s), 3.16 - 3.21 (4H, m), 3.58 - 3.62 (4H, m),
6.97 - 7.01 (2H, m), 7.27 - 7.32 (1H, m), 7.37 - 7.44

(2H, m), 7.50 - 7.58 (4H, m).

Reference Example 80

tert-butyl 4-(4-dimethylaminophenyl)piperazine-1-carboxylate

5 a white powder, yield 79%

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 2.87 (6H, s), 2.96 - 3.00 (4H, m), 3.54 - 3.59 (4H, m), 6.72 - 6.77 (2H, m), 6.87 - 6.92 (2H, m).

Reference Example 81

10 tert-butyl 4-(3-pyridyl)piperazine-1-carboxylate

a white powder, yield 99%

¹H-NMR (CDCl₃) δppm:

1.49 (9H, s), 3.14 - 3.19 (4H, m), 3.57 - 3.62 (4H, m), 7.17 - 7.19 (2H, m), 8.12 - 8.14 (1H, m), 8.31 - 8.33

15 (1H, m).

Reference Example 82

tert-butyl 4-(4-ethoxycarbonylphenyl)piperazine-1-carboxylate

a white powder, yield 42%

20 ¹H-NMR (CDCl₃) δppm:

1.37 (3H, t, J = 7.1 Hz), 1.48 (9H, s), 3.27 - 3.32 (4H, m), 3.56 - 3.60 (4H, m), 4.33 (2H, q, J = 7.1 Hz), 6.84 - 6.88 (2H, m), 7.92 - 7.96 (2H, m).

Reference Example 83

25 tert-butyl 4-(4-methylphenyl)piperazine-1-carboxylate

a white powder, yield 55%

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 2.27 (3H, s), 3.04 - 3.09 (4H, m), 3.55 -

3.59 (4H, m), 6.82 - 6.87 (2H, m), 7.06 - 7.10 (2H, m).

Reference Example 84

tert-butyl 4-(4-cyanophenyl)piperazine-1-carboxylate

a white powder, yield 86%

5 ^1H -NMR (CDCl_3) δ ppm:

1.49 (9H, s), 3.28 - 3.33 (4H, m), 3.56 - 3.60 (4H, m),
6.83 - 6.87 (2H, m), 7.49 - 7.53 (2H, m).

Reference Example 85

Preparation of 1-(4-trifluoromethylphenyl)piperazine

10 Tert-butyl 4-(4-trifluoromethylphenyl)-
piperazine-1-carboxylate (3.8 g, 11.5 mmol) prepared in
Reference Example 77 was dissolved in methylene
chloride (40 ml), to which trifluoroacetic acid (10 ml)
was added dropwise, and the mixture was stirred at room
15 temperature overnight. The reaction mixture was
concentrated under reduced pressure, and the residue
was neutralized with saturated sodium hydrogencarbonate
aqueous solution and the mixture was extracted with
methylene chloride. The extract was dried over
20 magnesium sulfate, and then filtered. The filtrate was
concentrated under reduced pressure to afford 1-(4-
trifluoromethylphenyl)piperazine (2.5 g, yield 96%) as
a white powder.

^1H -NMR (CDCl_3) δ ppm:

25 3.01 - 3.06 (4H, m), 3.21 - 3.26 (4H, m), 6.92 (2H, d,
 $J = 8.6$ Hz), 7.48 (2H, d, $J = 8.6$ Hz).

Using corresponding starting materials,
compounds of Reference Examples 86 to 89 were prepared

in the same manner as described in Reference Example 85.

Reference Example 86

1-(4-trifluoromethoxyphenyl)piperazine

5 a white powder, yield 100%

¹H-NMR (CDCl₃) δppm:

1.61 (1H, s), 3.00 - 3.05 (4H, m), 3.10 - 3.15 (4H, m),
6.85 - 6.92 (2H, m), 7.08 - 7.13 (2H, m).

Reference Example 87

10 1-(4-dimethylaminophenyl)piperazine

a white powder, yield 99%

¹H-NMR (CDCl₃) δppm:

1.60 (1H, br), 2.86 (6H, s), 3.01 (8H, br), 6.71 - 6.78
(2H, m), 6.87 - 6.92 (2H, m).

15 Reference Example 88

1-(3-pyridyl)piperazine

a white powder, yield 100%

¹H-NMR (CDCl₃) δppm:

2.09 (1H, s), 3.03 - 3.09 (4H, m), 3.14 - 3.20 (4H, m),
20 7.16 - 7.18 (2H, m), 8.09 - 8.11 (1H, m), 8.31 (1H, s).

Reference Example 89

1-(4-ethoxycarbonylphenyl)piperazine

a white powder, yield 95%

¹H-NMR (CDCl₃) δppm:

25 1.37 (3H, t, J = 7.1 Hz), 1.84 (1H, s), 3.00 - 3.04.
(4H, m), 3.26 - 3.31 (4H, m), 4.33 (2H, q, J = 7.1 Hz),
6.83 - 6.89 (2H, m), 7.89 - 7.96 (2H, m).

Reference Example 90

Preparation of tert-butyl 4-(piperazin-1-yl)benzoate

A mixture of tert-butyl 4-bromobenzoate (4.8 g, 18.8 mmol), piperazine (9.7 g, 0.11 mol), palladium acetate (85 mg, 0.38 mmol), (S)-(-)-BINAP (352 mg, 0.57 mmol), and sodium tert-butoxide (2.7 g, 28.2 mmol) in toluene (50 ml) was refluxed under a nitrogen atmosphere for 2 hours. Ethyl acetate and water were added to the reaction mixture and the insoluble substances were removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 5/1) to afford tert-butyl 4-(piperazin-1-yl) benzoate (3.8 g, yield 77%) as a gray powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.57 (9H, s), 3.00 - 3.04 (4H, m), 3.24 - 3.29 (4H, m), 6.83 - 6.87 (2H, m), 7.85 - 7.89 (2H, m).

Reference Example 91

Preparation of 4-trifluoromethoxybenzyl piperazine-1-carboxylate

To a solution of 4-trifluoromethoxybenzyl alcohol (25 g, 130.11 mmol) and phenyl chloroformate (20.37 g, 130.11 mmol) in ethyl acetate (125 ml), a solution of pyridine (11.6 ml, 143.12 mmol) in ethyl acetate (50 ml) was added dropwise below 15°C over 35

minutes. The mixture was stirred for 30 minutes. The reaction mixture was washed with water, 3 N hydrochloric acid, 10% potassium carbonate aqueous solution and brine, and dried over sodium sulfate. After
5 filtration, the filtrate was concentrated under reduced pressure to afford a carbonate compound as a colorless oil. To a solution of piperazine (33.62 g, 390.34 mmol) in methanol (125 ml), a solution of the carbonate compound in ethyl acetate (50 ml) was added dropwise
10 below 10°C over 25 minutes. The resulting mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford 4-
15 trifluoromethoxybenzyl piperazine-1-carboxylate (35.33 g, yield 89%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

2.57 - 2.96 (4H, m), 3.42 - 3.63 (4H, m), 5.13 (2H, s),
7.21 (2H, d, J = 8.5 Hz), 7.39 (2H, d, J = 8.5 Hz).

20 Reference Example 92

Preparation of 3-(4-trifluoromethylphenyl)-2-propenyl piperazine-1-carboxylate

A solution of pyridine (0.5 ml, 6.18 mmol) in ethyl acetate (2 ml) was gradually added dropwise to a
25 solution of 3-(4-trifluoromethylphenyl)-2-propen-1-ol (1 g, 4.95 mmol) and phenyl chloroformate (0.72 ml, 5.69 mmol) in ethyl acetate (5 ml) while cooling in an ice-bath. The mixture was stirred at room temperature

for 1 hour. The reaction mixture was washed with water, 3 N hydrochloric acid, 10% potassium carbonate aqueous solution and brine in this order, and dried over sodium sulfate. After filtration, the filtrate
5 was concentrated under reduced pressure to afford a carbonate compound as a colorless oil. To a solution of piperazine (1.28 g, 14.84 mmol) in methanol (5 ml), a solution of the carbonate compound in ethyl acetate (5 ml) was gradually added dropwise while cooling in an
10 ice-bath. The mixture was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford 3-(4-
15 trifluoromethylphenyl)-2-propenyl piperazine-1-carboxylate (1.4 g, yield 90%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

2.75 - 2.95 (4H, m), 3.43 - 3.57 (4H, m), 4.78 (2H, dd, J = 1.2 Hz, 6.0 Hz), 6.33 - 6.43 (1H, m), 6.66 (1H, d, 20 16.0 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz).

Using a corresponding starting material, a compound of Reference Example 93 was prepared in the same manner as described in Reference Example 92.

25 Reference Example 93

3-(4-Trifluoromethoxyphenyl)-2-propenyl piperazine-1-carboxylate
a colorless oil, yield 90%

¹H-NMR (CDCl₃) δppm:

2.75 - 2.88 (4H, m), 3.44 - 3.52 (4H, m), 4.75 (2H, dd,
J = 1.3 Hz, 6.2 Hz); 6.29 (1H, dt, J = 6.2 Hz, 15.9
Hz), 6.62 (1H, d, J = 15.9 Hz), 7.15 - 7.18 (2H, m),
5 7.38 - 7.42 (2H, m).

Reference Example 94

Preparation of 4-(4-chlorophenyl)-1,2,3,6-tetrahydro-
pyridine-1-carbonylchloride

A mixture of 4-(4-chlorophenyl)-1,2,3,6-
10 tetrahydropyridine hydrochloride (1 g, 4.3 mmol),
pyridine (680 mg, 8.6 mmol), and triphosgene (430 mg,
1.45 mmol) in toluene (20 ml) was heated under reflux
for 3 hours. The reaction mixture was allowed to
return to room temperature and diluted with diethyl
15 ether. The mixture was washed with 10% hydrochloric
acid, water and brine in this order, and dried over
magnesium sulfate. After filtration, the filtrate was
concentrated under reduced pressure to afford 4-(4-
chlorophenyl)-1,2,3,6-tetrahydropyridine-1-
20 carbonylchloride (1 g, yield 90%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

2.51 - 2.72 (2H, m), 3.81 - 4.00 (2H, m), 4.26 - 4.40
(2H, m), 5.93 - 6.09 (1H, m), 7.16 - 7.35 (4H, m).

Reference Example 95

25 Preparation of 1-benzyl-4-(4-trifluoromethylphenyl)-
piperidin-4-ol

4-Bromobenzotrifluoride (1 g, 4.44 mmol) was
dissolved in THF (15 ml), to which n-butyllithium (1.5

M) hexane solution (3.1 ml, 4.67 mmol) was added dropwise at -70°C. Then a solution of 1-benzyl-4-piperidone in THF (15 ml) was added dropwise to the mixture, and the resulting mixture was stirred for 2
5 hours and then at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica
10 gel column chromatography (n-hexane/acetone = 2/1) to afford 1-benzyl-4-(4-trifluoromethylphenyl)piperidin-4-ol (692 mg, yield 46%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

15 1.60 - 1.78 (2H, m), 2.07 - 2.25 (2H, m), 2.38 - 2.54 (2H, m), 2.74 - 2.87 (2H, m), 3.59 (2H, s), 7.20 - 7.38 (5H, m), 7.51 - 7.67 (4H, m).

Reference Example 96

Preparation of 1-benzyl-4-(4-trifluoromethylphenyl)-
20 1,2,3,6-tetrahydropyridine

A mixture of 1-benzyl-4-(4-trifluoromethylphenyl)piperidin-4-ol (692 mg, 2.06 mmol) prepared in Reference Example 95, concentrated hydrochloric acid (4.5 ml) and acetic acid (10 ml) was heated under
25 reflux overnight. The reaction mixture was allowed to return to room temperature, and diluted with methylene chloride. The mixture was washed with water, 10% sodium hydroxide aqueous solution and brine, and dried

over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/acetone = 4/1) to afford 1-benzyl-4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine (528 mg, yield 80%) as a pale yellow crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

2.50 - 2.60 (2H, m), 2.62 - 2.76 (2H, m), 3.11 - 3.22 (2H, m), 3.65 (2H, s), 6.10 - 6.20 (1H, m), 7.20 - 7.54 (9H, m).

Reference Example 97

Preparation of 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride

1-Benzyl-4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine (2 g, 6.3 mmol) prepared in Reference Example 96 was dissolved in methylene chloride (20 ml), to which 2-chloroethyl chloroformate (1.67 g, 11.68 mmol) was added dropwise under a nitrogen atmosphere while cooling in an ice-bath, and the mixture was stirred at the same temperature for 3 hours. Methanol (20 ml) was added to the mixture, which was heated under reflux for 1 hour. The reaction mixture was allowed to return to room temperature, to which diethyl ether was added, and the resulting precipitates were collected by filtration to afford 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride (1.44 g, yield 87%) as a colorless crystalline powder.

¹H-NMR (DMSO-d₆) δppm:

2.64 - 2.80 (2H, m), 3.18 - 3.34 (2H, m), 3.68 - 3.80 (2H, m), 6.25 - 6.39 (1H, m), 7.61 - 7.80 (4H, m).

Reference Example 98

- 5 Preparation of 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride

Using 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride (300 mg, 1.14 mmol) prepared in Reference Example 97, pyridine (0.18 ml, 2.28 mmol) and triphosgene (112 mg, 0.38 mmol), 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride (220 mg, yield 67%) as a yellow oil was prepared in the same manner as described in Reference Example 94.

- 15 ¹H-NMR (CDCl₃) δppm:

2.57 - 2.75 (2H, m), 3.82 - 4.00 (2H, m), 4.25 - 4.40 (2H, m), 6.05 - 6.16 (1H, m), 7.47 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz).

Reference Example 99

- 20 Preparation of 4-(4-chlorophenyl)piperidine hydrochloride

A mixture of 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (2 g, 8.7 mmol) and platinum oxide (100 mg) in ethanol (100 ml) was stirred at room temperature under an atmospheric pressure of hydrogen. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The resulting precipitates by treating the

residue with diethyl ether were collected by filtration to afford 4-(4-chlorophenyl) piperidine hydrochloride (1.9 g, yield 94%) as a pale gray powder.

¹H-NMR (DMSO-d₆) δppm:

5 1.75 - 1.95 (4H, m), 2.74 - 3.05 (3H, m), 3.25 - 3.44 (2H, m), 7.25 (2H, d, J = 8.5 Hz), 7.38 (2H, d, J = 8.5 Hz).

Reference Example 100

Preparation of 4-(4-trifluoromethylphenyl)piperidine

10 A mixture of 1-benzyl-4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine (528 mg, 1.66 mmol) prepared in Reference Example 96 and 10% palladium/carbon (50 mg) in acetic acid (5 ml) was stirred at room temperature under an atmospheric
15 pressure of hydrogen. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methylene chloride, and the mixture was washed with water, 10% sodium hydroxide aqueous
20 solution and brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 4-(4-trifluoromethylphenyl)piperidine (400 mg, quantitative) as a yellow oil.

25 ¹H-NMR (CDCl₃) δppm:

1.72 - 2.00 (4H, m), 2.61 - 2.84 (3H, m), 3.07 - 3.27 (2H, m), 7.32 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz).

Reference Example 101

Preparation of 4-(4-trifluoromethylphenyl)piperidine-1-carbonylchloride

Using 4-(4-trifluoromethylphenyl)piperidine
5 (760 mg, 3.32 mmol) prepared in Reference Example 100, 4-(4-trifluoromethylphenyl)piperidine-1-carbonylchloride (crude product) a pale brown oil was prepared in the same manner as described in Reference Example 94.

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.65 - 1.84 (2H, m), 1.86 - 2.02 (2H, m), 2.77 - 3.28 (3H, m), 4.42 - 4.60 (2H, m), 7.32 (2H, d, $J = 8.1$ Hz), 7.59 (2H, d, $J = 8.1$ Hz).

Reference Example 102

15 Preparation of 2-[3-(4-trifluoromethylphenyl)-2-propenyl]phthalimide

4-(Trifluoromethyl)cinnamyl alcohol (3 g, 14.84 mmol) was dissolved in THF (60 ml), and phthalimide (2.84 g, 19.29 mmol) and triphenylphosphine
20 (5.84 g, 22.26 mmol) were added to the solution, to which a solution of diethyl azodicarboxylate (3.87 g, 22.26 mmol) in THF (20 ml) was gradually added dropwise. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated
25 under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/methylene chloride = 1/1) to afford 2-[3-(4-trifluoro-methylphenyl)-2-propenyl]phthalimide (4.57 g, yield

93%) as a white powder.

^1H -NMR (CDCl_3) δ ppm:

4.47 (2H, dd, $J = 1.2$ Hz, 6.3 Hz), 6.27 - 6.41 (1H, m),
6.68 (1H, d, $J = 15.9$ Hz), 7.44 (2H, d, $J = 8.4$ Hz),
5 7.54 (2H, d, $J = 8.4$ Hz), 7.74 (2H, dd, $J = 2.0$ Hz, 7.0
Hz), 7.85 (2H, dd, $J = 2.0$ Hz, 7.0 Hz).

Reference Example 103

Preparation of 3-(4-trifluoromethylphenyl)-2-propenylamine

10 A mixture of 2-[3-(4-trifluoromethylphenyl)-
2-propenyl]phthalimide (4.57 g, 13.79 mmol) prepared in
Reference Example 102 and hydrazine hydrate (897 mg,
17.93 mmol) in ethanol (80 ml) was heated under reflux
for 3 hours. The reaction mixture was allowed to
15 return to room temperature and filtered, and the
filtrate was concentrated under reduced pressure. To
the residue, ethyl acetate was added, and the resulting
mixture was washed with 1 N sodium hydroxide aqueous
solution and brine, and dried over magnesium sulfate.
20 After filtration, the filtrate was concentrated under
reduced pressure to afford 3-(4-
trifluoromethylphenyl)-2-propenylamine (2.78 g,
quantitative) as a pale brown crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

25 3.51 (2H, d, $J = 4.7$ Hz), 6.31 - 6.47 (1H, m), 6.55
(1H, d, $J = 16.0$ Hz), 7.45 (2H, d, $J = 8.3$ Hz), 7.55
(2H, d, $J = 8.3$ Hz).

Reference Example 104

Preparation of piperazin-1-yl-(5-chlorobenzofuran-2-yl methylene)amine

1-Aminopiperazine (29 g, 287 mmol) was dissolved in isopropyl alcohol (173 ml), to which 5-chlorobenzofuran-2-aldehyde (34.52 g, 191 mmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to afford piperazin-1-yl-(5-chlorobenzofuran-2-yl methylene)amine (49.49 g, yield 98%) as a yellow crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.95 - 3.10 (4H, m), 3.17 - 3.29 (4H, m), 6.70 (1H, s), 7.20 (1H, dd, $J = 2.1 \text{ Hz}, 8.7 \text{ Hz}$), 7.38 - 7.52 (3H, m).

Reference Example 105

Preparation of piperazin-1-yl-(4-trifluoromethyl benzylidene)amine

Tert-butyl piperazin-1-yl-carbamate (403 mg, 2.0 mmol) was suspended in methylene chloride (4 ml), to which trifluoroacetic acid (1.6 ml) was added, and the mixture was stirred at room temperature for 5 minutes. To which 4-(trifluoromethyl)benzaldehyde (0.3 ml, 2.2 mmol) was added, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into sodium hydrogencarbonate aqueous solution, and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and then concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (methylene chloride/methanol = 9/1) to afford piperazin-1-yl-(4-trifluoromethylbenzylidene)-amine (432 mg, yield 84%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.00 - 3.29 (8H, m), 7.43 - 7.62 (3H, m), 7.68 (2H, d, $J = 8.2$ Hz).

Reference Example 106

10 Preparation of piperazin-1-yl-(4-trifluoromethoxybenzylidene)amine

To a solution of 4-benzylpiperazin-1-yl-amine (43.18 g, 225 mmol) in ethanol (400 ml), a suspension of 20% palladium hydroxide/carbon (6.50 g) in ethanol (30 ml) was added, and the mixture was stirred at room temperature under an atmospheric pressure of hydrogen for 3 hours and then at 50°C for 2 hours. The reaction mixture was filtered through Celite, 4-(trifluoromethoxy)benzaldehyde (42.92 g, 225 mmol) was added to the filtrate, and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford piperazin-1-yl-(4-trifluoromethoxybenzylidene)amine (56.88 g, yield 93%) as a pale yellow crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.00 - 3.23 (8H, m), 7.18 (2H, d, $J = 8.7$ Hz), 7.58 (1H, s), 7.62 (2H, d, $J = 8.7$ Hz).

Using a corresponding starting material, a compound of Reference Example 107 was prepared in the same manner as described in Reference Example 106.

Reference Example 107

piperazin-1-yl-(5-trifluoromethylbenzofuran-2-yl methylene)amine

a pale yellow crystalline powder, yield 77%

^1H -NMR (CDCl_3) δ ppm:

3.00 - 3.14 (4H, m), 3.23 - 3.32 (4H, m), 6.79 (1H, s), 7.41 - 7.59 (3H, m), 7.82 (1H, s).

Reference Example 108

Preparation of (4-benzylpiperazin-1-yl)-(4-trifluoromethylphenyl)amine

A mixture of 4-bromobenzotrifluoride (3.00 g, 13.3 mmol), 4-benzylpiperazin-1-yl-amine (3.06 g, 16.0 mmol), palladium acetate (60 mg, 0.267 mmol), (S)-(-)-BINAP (174 mg, 0.280 mmol) and sodium tert-butoxide (1.92 g, 20.0 mmol) in toluene (60 ml) was refluxed under a nitrogen atmosphere for 7 hours. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (n-hexane/acetone = 4/1) to afford (4-benzylpiperazin-1-yl)-(4-

trifluoromethylphenyl)amine (2.666 g, yield 59%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.58 (4H, br), 2.76 (4H, br), 3.55 (2H, s), 4.65 (1H, br), 6.90 (2H, d, $J = 8.6$ Hz), 7.23 - 7.35 (5H, m), 7.41 (2H, d, $J = 8.6$ Hz).

Reference Example 109

Preparation of piperazin-1-yl-(4-trifluoromethylphenyl)amine

10 A mixture of (4-benzylpiperazin-1-yl)-(4-trifluoromethylphenyl)amine prepared in Reference Example 108 and 10% palladium/carbon (0.53 g) in ethanol (50 ml) was stirred at room temperature under an atmospheric pressure of hydrogen for 6 hours, and
15 then at 60°C for 10 hours. After the catalyst was removed by filtration through Celite, 10% palladium/carbon (0.53 g) was added to the filtrate, and the mixture was stirred at 60°C under an atmospheric pressure of hydrogen for 8 hours. After the catalyst
20 was removed by filtration through Celite, the filtrate was concentrated under reduced pressure. The resulting solid was dried *in vacuo* to afford piperazin-1-yl-(4-trifluoromethylphenyl)amine (1.76 g, yield 90%) as a colorless crystalline powder.

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

2.71 (4H, br), 3.00 (4H, t, $J = 4.8$ Hz), 4.71 (1H, br), 6.92 (2H, d, $J = 8.5$ Hz), 7.42 (2H, d, $J = 8.5$ Hz).

Reference Example 110

Preparation of tert-butyl 4-(3-phenyl-2-propenyloxy)-
piperidine-1-carboxylate

Tert-butyl 4-hydroxypiperidine-1-carboxylate
(0.396 g, 1.97 mmol) was dissolved in DMF (5 ml), to
5 which sodium hydride (0.086 g, 2.16 mmol) was added,
and the mixture was stirred at room temperature for 1
hour. Cinnamyl chloride (0.300 g, 1.97 mmol) was added
to the mixture while cooling in an ice-bath, and the
resulting mixture was stirred overnight. The reaction
10 mixture was diluted with ethyl acetate, and the mixture
was washed with water and brine. The organic layer was
dried over magnesium sulfate, and then filtered, and
the filtrate was concentrated under reduced pressure.
The residue was purified by silica gel column
15 chromatography (n-hexane/ethyl acetate = 6/1) to afford
tert-butyl 4-(3-phenyl-2-propenyloxy)piperidine-1-
carboxylate (0.314 g, yield 50%) as a yellow oil.

^1H -NMR (CDCl_3) δ ppm:

1.46 (9H, s), 1.48 - 1.59 (2H, m), 1.81 - 1.93 (2H, m),
20 3.01 - 3.15 (2H, m), 3.50 - 3.61 (1H, m), 3.74 - 3.87
(2H, m), 4.19 (2H, d, $J = 5.9$ Hz), 6.29 (1H, ddd, $J =$
5.9 Hz, 5.9 Hz, 15.9 Hz), 6.61 (1H, d, $J = 15.9$ Hz),
7.18 - 7.43 (5H, m).

Reference Example 111

25 Preparation of 4-(3-phenyl-2-propenyloxy)piperidine

Tert-butyl 4-(3-phenyl-2-propenyloxy)-
piperidine-1-carboxylate (0.314 g, 0.989 mmol) prepared
in Reference Example 110 was dissolved in ethanol (10

ml), to which 6N hydrochloric acid aqueous solution(3 ml, 18 mmol) was added, and the mixture was stirred at 60°C for 1 hour. The reaction mixture was neutralized with sodium hydroxide aqueous solution, and the mixture
5 was extracted with methylene chloride. The extract was washed with brine, dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was dried *in vacuo* to afford 4-(3-phenyl-2-propenyloxy)piperidine (0.198 g, yield
10 92%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.40 - 1.57 (2H, m), 1.91 - 2.02 (2H, m), 2.56 - 2.70 (2H, m), 3.12 (2H, ddd, J = 4.2 Hz, 4.2 Hz, 12.8 Hz), 3.42 - 3.52 (1H, m), 4.19 (2H, d, J = 5.9 Hz), 6.30
15 (1H, ddd, J = 5.9 Hz, 5.9 Hz, 15.9 Hz), 6.57 (1H, d, J = 15.9 Hz), 7.20 - 7.43 (5H, m).

Reference Example 112

Preparation of tert-butyl 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine-1-carboxylate

20 Tert-butyl 4-hydroxypiperidine-1-carboxylate (3.58 g, 17.8 mmol) was dissolved in DMF (30 ml), to which sodium hydride (0.71 g, 17.8 mmol) was added, and the mixture was stirred at room temperature for 2 hours.

25 On the other hand, 4-chlorocinnamyl alcohol (3.00 g, 17.8 mmol) was dissolved in methylene chloride (60 ml), to which triethyl amine (5 ml, 35.6 mmol) and methanesulfonyl chloride (2.1 ml, 26.7 mmol) were added

dropwise while cooling in an ice-bath, the mixture was stirred at room temperature for 1.5 hours. Water was added to the mixture, which was extracted with methylene chloride, and the extract was washed with dilute hydrochloric acid solution, sodium bicarbonate aqueous solution and brine. The organic layer was dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (10 ml).

Both the DMF solutions were combined while cooling in an ice-bath, and the mixture was stirred overnight. After the reaction mixture was diluted with ethyl acetate, the mixture was washed with water and brine. The organic layer was dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 6/1) to afford tert-butyl 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine-1-carboxylate (0.759 g, yield 12%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 1.50 - 1.62 (2H, m), 1.83 - 1.94 (2H, m), 3.03 - 3.14 (2H, m), 3.53 - 3.58 (1H, m), 3.77 - 3.83 (2H, m), 4.17 (1H, d, J = 5.7 Hz), 4.18 (1H, d, J = 5.7 Hz), 6.27 (1H, ddd, J = 5.7 Hz, 5.7 Hz, 15.9 Hz), 6.57 (1H, d, J = 15.9 Hz), 7.20 - 7.33 (4H, m).

Reference Example 113

Preparation of 4-[3-(4-chlorophenyl)-2-propenyloxy]-

piperidine

Using tert-butyl 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine-1-carboxylate (0.350 g, 0.995 mmol) prepared in Reference Example 112, 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine (0.291 g, quantitative) as a brown oil was prepared in the same manner as described in Reference Example 111.

^1H -NMR (CDCl_3) δ ppm:

1.38 - 1.56 (2H, m), 1.91 - 2.01 (2H, m), 2.55 - 2.69 (2H, m), 3.11 (2H, ddd, $J = 4.0$ Hz, 4.0 Hz, 13.0 Hz), 3.39 - 3.51 (1H, m), 4.18 (2H, d, $J = 5.8$ Hz), 6.28 (1H, ddd, $J = 5.8$ Hz, 5.8 Hz, 15.9 Hz), 6.57 (1H, d, $J = 15.9$ Hz), 7.25 - 7.35 (4H, m).

Reference Example 114

Preparation of tert-butyl 4-[3-(4-chlorophenyl)propoxy]piperidine-1-carboxylate

A mixture of tert-butyl 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine-1-carboxylate (0.37 g, 1.05 mmol) prepared in Reference example 112 and platinum oxide (37 mg) in ethanol (10 ml), was stirred at room temperature under atmospheric pressure of hydrogen. The reaction mixture was filtered through Celite, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford tert-butyl 4-[3-(4-chlorophenyl)propoxy]piperidine-1-carboxylate (0.151 g, yield 40%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.40 - 1.51 (2H, m), 1.46 (9H, s), 1.77 - 1.90 (4H, m),
2.67 (2H, t, J = 7.9 Hz), 3.02 - 3.12 (2H, m), 3.38 -
3.45 (3H, m), 3.73 - 3.79 (2H, m), 7.11 (2H, d, J = 8.4
5 Hz), 7.24 (1H, d, J = 8.4 Hz).

Reference Example 115

Preparation of 4-[3-(4-chlorophenyl) propoxy]piperidine

Tert-butyl 4-[3-(4-chlorophenyl) propoxy]-
piperidine-1-carboxylate (0.151 g, 0.427 mmol) prepared
10 in Reference example 114 was dissolved in methylene
chloride (4 ml), to which trifluoroacetic acid was
added, and the mixture was stirred at room temperature
overnight. The reaction mixture was neutralized with
sodium hydroxide aqueous solution, and the mixture was
15 extracted with methylene chloride twice. The extracts
were combined and washed with brine. The organic layer
was dried over sodium sulfate, and then filtered. The
filtrate was concentrated under reduced pressure, and
the residue was dried *in vacuo* to afford 4-[3-(4-
20 chlorophenyl) propoxy]piperidine (0.109 g, yield 92%)
as a brown oil.

¹H-NMR (CDCl₃) δppm:

1.35 - 1.51 (2H, m), 1.83 - 1.94 (4H, m), 2.54 - 2.70
(4H, m), 3.03 - 3.14 (2H, m), 3.22 - 3.38 (1H, m), 3.43
25 (2H, t, J = 6.3 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.25
(2H, d, J = 8.4 Hz).

Reference Example 116

Preparation of tert-butyl 4-[2-(4-chlorophenyl)

ethoxy]piperidine-1-carboxylate

(4-Chlorobenzyl)triphenyl phosphonium chloride (1.191 g, 2.81 mmol) was dissolved in DMSO (20 ml), to which sodium hydride (0.118 g, 2.95 mmol) was
5 added while cooling in an ice-bath, and the mixture was stirred at room temperature for 1 hour. Tert-butyl 4-formyloxypiperidine-1-carboxylate (0.500 g, 2.34 mmol) was added to the mixture, and the resulting mixture was stirred at room temperature overnight. After the
10 reaction mixture was diluted with ethyl acetate, the mixture was washed with water and brine. The organic layer was dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
15 column chromatography (methylene chloride/hexane = 9/1) to afford a colorless oil.

Using thus obtained oil, tert-butyl 4-[2-(4-chlorophenyl) ethoxy]piperidine-1-carboxylate (0.127 g, yield 16%) as a colorless oil was prepared in the same
20 manner as described in Reference Example 114.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.40-1.51 (2H, m), 1.45 (9H, s), 1.71 - 1.79 (2H, m),
2.83 (2H, t, $J = 6.9$ Hz), 3.02 - 3.13 (2H, m), 3.38 -
3.44 (1H, m), 3.62 - 3.75 (4H, m), 7.15 (2H, d, $J = 8.5$
25 Hz), 7.25 (2H, d, $J = 8.5$ Hz).

Reference Example 117

Preparation of 4-[2-(4-chlorophenyl) ethoxy]piperidine

Using tert-butyl 4-[2-(4-chlorophenyl)

ethoxy]piperidine-1-carboxylate (0.127 g, 0.374 mmol) prepared in Reference Example 116, 4-[2-(4-chlorophenyl)ethoxy]piperidine (0.080 g, yield 89%) as a colorless oil was prepared in the same manner as described in Reference Example 115.

¹H-NMR (CDCl₃) δppm:

1.37 - 1.48 (2H, m), 1.84 - 1.91 (2H, m), 2.53 - 2.63 (2H, m), 2.83 (2H, t, J = 7.0 Hz), 3.01 - 3.09 (2H, m), 3.25 - 3.41 (1H, m), 3.64 (2H, t, J = 7.0 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.4 Hz).

Reference Example 118

Preparation of 1-(2-nitrovinyl)-4-trifluoromethylbenzene

4-Trifluoromethylbenzaldehyde (3.00 g, 17.2 mmol) was dissolved in nitromethane (10 ml), to which ammonium acetate (1.341 g, 17.4 mmol) was added, and the mixture was heated under reflux for 2 hours. Water was added to the mixture, which was extracted with methylene chloride twice, and the extracts were combined and washed with brine, and dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 9/1) to afford 1-(2-nitrovinyl)-4-trifluoromethylbenzene (1.596 g, yield 43%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

7.58 - 7.74 (5H, m), 8.02 (1H, d, J = 13.8 Hz).

Reference Example 119

Preparation of 2-(4-trifluoromethylphenyl) ethylamine

Lithium aluminum hydride (0.558 g, 14.7 mmol) was suspended in THF (10 ml), to which a solution of 1-(2-nitrovinyl)-4-trifluoromethylbenzene (1.596 g, 7.35 mmol) prepared in Reference Example 118 in THF (10 ml) was added dropwise while cooling in an ice-bath, and the mixture was heated under reflux for 2 hours. Methanol was slowly added to the mixture until it no longer foamed. Water (0.6 ml), 15% sodium hydroxide aqueous solution (0.6 ml) and water (1.8 ml) were added in this order, and the insoluble substances were removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with an amine-treated surface (Fuji Silysia ; NH-DM1020, solvent ; methylene chloride/n-hexane = 4/1) to afford 2-(4-trifluoromethylphenyl) ethylamine (0.431 g, yield 31%) as an orange-colored oil.

¹H-NMR (CDCl₃) δppm:

2.81 (2H, t, J = 6.9 Hz), 3.03 (2H, t, J = 6.9 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.56 (2H, d, J = 8.0 Hz).

Reference Example 120

Preparation of tert-butyl N-(1-benzylpiperidin-4-yl)-N-[2-(4-trifluoromethylphenyl) ethyl]carbamate

2-(4-Trifluoromethylphenyl)ethylamine (0.431 g, 2.28 mmol) prepared in Reference Example 119 and 1-benzyl-4-piperidone (0.517 g, 2.73 mmol) were dissolved

in methanol (15 ml), to which sodium cyanoborohydride (0.429 g, 6.83 mmol) and acetic acid (0.52 ml, 9.11 mmol) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed with saturated sodium bicarbonate aqueous solution and brine. The organic layer was dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (5 ml), to which di-tert-butyl dicarbonate (0.597 g, 2.74 mmol) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with brine. The organic layer was dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) to afford tert-butyl N-(1-benzylpiperidin-4-yl)-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate (0.437 g, yield 41%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.55 (9H, s), 1.59 - 1.73 (4H, m), 1.90 - 2.10 (2H, m), 2.82 - 2.96 (4H, m), 3.24 - 3.28 (2H, m), 3.49 (2H, s), 4.00 (1H, bs), 7.26 - 7.31 (7H, m), 7.54 (2H, d, $J = 8.0$ Hz).

Reference Example 121

Preparation of tert-butyl N-(piperidin-4-yl)-N-[2-(4-trifluoromethylphenyl) ethyl]carbamate

A mixture of tert-butyl N-(1-benzylpiperidin-4-yl)-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate

- 5 (0.437 g, 0.944 mmol) prepared in Reference Example 120 and 20% palladium hydroxide/carbon (100 mg) in ethanol (20 ml) was stirred at room temperature under an atmospheric pressure of hydrogen. The reaction mixture was filtered through Celite, and the filtrate was
- 10 concentrated under reduced pressure to afford tert-butyl N-(piperidin-4-yl)-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate (0.332 g, yield 94%) as a colorless oil.

^1H -NMR (CDCl_3) δ ppm:

- 15 1.49 (9H, s), 1.51 - 1.80 (4H, m), 2.62 - 3.49 (9H, m), 7.28 - 7.31 (2H, m), 7.54 (2H, d, $J = 8.0$ Hz).

Reference Example 122

Preparation of tert-butyl 4-(4-trifluoromethylbenzyloxy)piperidine-1-carboxylate

- 20 Tert-butyl 4-hydroxypiperidine-1-carboxylate (1.88 g, 9.34 mmol) was dissolved in THF (20 ml). Sodium hydride (411 mg, 10.3 mmol) was added to this solution while cooling in an ice-bath, and the mixture was stirred for 1 hour. 4-(Trifluoromethyl)
- 25 benzylbromide (2.23 g, 9.34 mmol) was added to the mixture, which was stirred at room temperature for 2 hours. Water was added to the reaction mixture, which was extracted with methylene chloride. The extract was

dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to
5 afford tert-butyl 4-(4-trifluoromethylbenzyloxy)piperidine-1-carboxylate (2.56 g, yield 76%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 1.51 - 1.67 (2H, m), 1.83 - 1.91 (2H, m),
10 3.07 - 3.18 (2H, m), 3.52 - 3.63 (1H, m), 3.73 - 3.83 (2H, m), 4.61 (2H, m), 7.46 (2H, d, J = 8.2 Hz), 7.60 (2H, d, J = 8.2 Hz).

Using a corresponding starting material, a compound of Reference Example 123 was prepared in the
15 same manner as described in Reference Example 122.

Reference Example 123

tert-butyl 4-(4-trifluoromethoxybenzyloxy)piperidine-1-carboxylate

a pale yellow oil, yield 74%

20 ¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 1.51 - 1.65 (2H, m), 1.82 - 1.90 (2H, m),
3.06 - 3.17 (2H, m), 3.52 - 3.62 (1H, m), 3.73 - 3.83 (2H, m), 4.54 (2H, s), 7.17 - 7.20 (2H, m), 7.35 - 7.38 (2H, m).

25 Reference Example 124

Preparation of 4-(4-trifluoromethylbenzyloxy)piperidine

Tert-butyl 4-(4-trifluoromethylbenzyloxy)-piperidine-1-carboxylate (2.56 g, 7.12 mmol) prepared

in Reference Example 122 was dissolved in methylene chloride (20 ml), to which trifluoroacetic acid (10 ml) was added dropwise, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was then dissolved in methylene chloride. This solution was neutralized with sodium hydroxide aqueous solution and the mixture was extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 4-(4-trifluoromethylbenzyloxy)piperidine (1.85 g, yield 99%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 - 1.60 (2H, m), 1.87 (1H, s), 1.93 - 2.01 (2H, m), 2.58 - 2.69 (2H, m), 3.07 - 3.16 (2H, m), 3.43 - 3.54 (1H, m), 4.61 (2H, s), 7.44 - 7.48 (2H, m), 7.57 - 7.61 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 125 to 128 were prepared in the same manner as described in Reference Example 124.

Reference Example 125

4-(4-trifluoromethoxybenzyloxy)piperidine
a white powder, yield 74%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.45 - 1.60 (2H, m), 1.92 - 2.02 (2H, m), 2.11 (1H, s), 2.59 - 2.70 (2H, m), 3.07 - 3.17 (2H, m), 3.43 - 3.54

(1H, m), 4.55 (2H, s), 7.17 - 7.20 (2H, m), 7.35 - 7.40 (2H, m).

Reference Example 126

4-(4-chlorobenzyloxy)piperidine

5 a white powder, yield 94%

¹H-NMR (CDCl₃) δppm:

1.39 - 1.56 (3H, m), 1.90 - 1.99 (2H, m), 2.55 - 2.66 (2H, m), 3.06 - 3.11 (2H, m), 3.39 - 3.51 (1H, m), 4.52 (2H, s), 7.25 - 7.33 (4H, m).

10

Reference Example 127

4-(3,4-dichlorobenzyloxy)piperidine

a white powder, yield 99%

¹H-NMR (CDCl₃) δppm:

1.45 - 1.60 (2H, m), 1.91 - 2.01 (2H, m), 2.19 (1H, s),
15 2.59 - 2.70 (2H, m), 3.07 - 3.16 (2H, m), 3.42 - 3.52 (1H, m), 4.50 (2H, s), 7.17 (1H, dd, J = 1.9 Hz, 8.2 Hz), 7.40 (1H, d, J = 8.2 Hz), 7.45 (1H, d, J = 1.9 Hz).

Reference Example 128

20 4-(4-phenylbenzyloxy)piperidine

a white powder, yield 16%

¹H-NMR (CDCl₃) δppm:

1.45 - 1.60 (2H, m), 1.72 (1H, s), 1.95 - 2.02 (2H, m),
2.57 - 2.68 (2H, m), 3.07 - 3.16 (2H, m), 3.45 - 3.56
25 (1H, m), 4.60 (2H, s), 7.25 - 7.60 (9H, m).

Reference Example 129

Preparation of (1-benzylpiperidin-4-yl)-(4-trifluoro-methoxyphenyl)amine

A mixture of 1-bromo-4-trifluoromethoxybenzene (2.0 g, 8.3 mmol), 4-amino-1-benzylpiperidine (1.73 g, 9.13 mmol), palladium acetate (37 mg, 0.17 mmol), (R)-(+)-BINAP (155 mg, 0.25 mmol) and sodium tert-butoxide (1.2 g, 11.6 mmol) in toluene (30 ml) was refluxed under a nitrogen atmosphere for 5 hours. Ethyl acetate and water were added to the reaction mixture while stirring, the insoluble substances were removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford (1-benzylpiperidin-4-yl)-(4-trifluoromethoxyphenyl)amine (3.0 g, yield 99%) as a dark oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.39 - 1.55 (2H, m), 1.98 - 2.05 (2H, m), 2.09 - 2.20 (2H, m), 2.80 - 2.89 (2H, m), 3.21 - 3.28 (1H, m), 3.52 (2H, s), 3.52 - 3.59 (1H, m), 6.48 - 6.55 (2H, m), 6.98 - 7.02 (2H, m), 7.22 - 7.33 (5H, m).

Reference Example 130

Preparation of piperidin-4-yl-(4-trifluoromethoxyphenyl)amine

A mixture of (1-benzylpiperidin-4-yl)-(4-trifluoromethoxyphenyl)amine (3.0 g, 8.3 mmol) prepared in Reference Example 129 and a catalytic amount of 10%

palladium/carbon in ethanol (30 ml) was refluxed under an atmospheric pressure of hydrogen for 20 hours. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The
5 residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford piperidin-4-yl-(4-trifluoromethoxyphenyl)amine (2.02 g, yield 94%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

10 1.24 - 1.39 (2H, m), 2.03 - 2.08 (2H, m), 2.65 - 2.77 (2H, m), 3.08 - 2.16 (2H, m), 3.24 - 3.41 (1H, m), 3.59 (1H, br), 6.50 - 6.58 (2H, m), 6.99 - 7.03 (2H, m).

Reference Example 131

Preparation of tert-butyl 4-(4-chlorophenylamino)-
15 piperidine-1-carboxylate

A mixture of p-bromochlorobenzene (1.91 g, 9.99 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (2.0 g, 9.99 mmol), palladium acetate (45 mg, 0.2 mmol), (R)-(+)-BINAP (187 mg, 0.3 mmol) and sodium
20 tert-butoxide (1.35 g, 14.0 mmol) in toluene (20 ml) was refluxed under a nitrogen atmosphere for 1 hour. Ethyl acetate and water were added to the reaction mixture while stirring, the insoluble substances were removed by filtration through Celite, and the filtrate
25 was then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by

silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(4-chlorophenylamino)piperidine-1-carboxylate (2.67 g, yield 86%) as a yellow powder.

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.21 - 1.54 (2H, m) 1.46 (9H, s), 1.99 - 2.05 (2H, m),
2.85 - 2.97 (2H, m), 3.37 (1H, br), 3.51 (1H, br), 4.01
- 4.07 (2H, m), 6.48 - 6.54 (2H, m), 7.07 - 7.14 (2H,
m).

10 Using corresponding starting materials,
compounds of Reference Examples 132 to 133 were
prepared in the same manner as described in Reference
Example 131.

Reference Example 132

15 tert-butyl 4-(4-trifluoromethylphenylamino)piperidine-
1-carboxylate

a yellow powder, yield 93%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.21 - 1.58 (2H, m), 1.47 (9H, s), 2.00 - 2.06 (2H, m),
20 2.88 - 2.99 (2H, m), 3.47 (1H, br), 3.88 (1H, bs), 4.03
- 4.09 (1H, m), 6.56 (2H, d, $J = 8.6$ Hz), 7.39 (2H, d,
 $J = 8.6$ Hz).

Reference Example 133

tert-butyl 4-(4-cyanophenylamino)piperidine-1-
25 carboxylate

a yellow powder, yield 92%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.26 - 1.54 (2H, m), 1.47 (9H, s), 1.99 - 2.05 (2H, m),

2.87 - 2.99 (2H, m), 3.41 - 3.53 (1H, br), 4.02 - 4.14 (3H, m), 6.52 - 6.58 (2H, m), 7.39 - 7.45 (2H, m).

Reference Example 134

Preparation of 4-(4-chlorophenylamino)piperidine

5 Tert-butyl 4-(4-chlorophenylamino)piperidine-1-carboxylate (2.67 g, 8.59 mmol) prepared in Reference Example 131 was dissolved in methylene chloride (20 ml), to which trifluoroacetic acid (15 ml) was added dropwise, and the mixture was stirred at room
10 temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was then dissolved in methylene chloride. This solution was neutralized with sodium hydroxide aqueous solution, and the mixture was extracted with methylene
15 chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 4-(4-chlorophenylamino)piperidine as a pale yellow powder.

20 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.22 - 1.38 (2H, m), 2.02 - 2.07 (2H, m), 2.65 - 2.76 (2H, m), 3.08 - 3.16 (2H, m), 3.25 - 3.38 (1H, m), 3.50 - 3.54 (1H, m), 6.48 - 6.55 (2H, m), 7.06 - 7.26 (2H, m).

25 Using corresponding starting materials, compounds of Reference Examples 135 to 136 were prepared in the same manner as described in Reference Example 134.

Reference Example 135

4-(4-trifluoromethylphenylamino)piperidine

a yellow powder, yield 97%

¹H-NMR (CDCl₃) δppm:

5. 1.26 - 1.42 (2H, m), 2.04 - 2.09 (2H, m), 2.67 - 2.78 (2H, m), 3.09 - 3.17 (2H, m), 3.34 - 3.46 (1H, m), 3.86 - 3.90 (1H, m), 6.59 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz).

Reference Example 136

10 4-(4-cyanophenylamino)piperidine

a yellow powder, yield 98%

¹H-NMR (CDCl₃) δppm:

- 1.27 - 1.45 (2H, m), 2.02 - 2.07 (2H, m), 2.67 - 2.78 (2H, m), 3.09 - 3.17 (2H, m), 3.34 - 3.46 (1H, m), 4.09
15 - 4.13 (1H, m), 6.51 - 6.57 (2H, m), 7.38 - 7.44 (2H, m).

Reference Example 137

Preparation of tert-butyl 4-(toluene-4-sulfonyloxy)-piperidine-1-carboxylate

- 20 Tert-butyl 4-hydroxypiperidine-1-carboxylate (2.22 g, 10.0 mmol) was dissolved in acetonitrile (40 ml), to which triethylamine (2.74 ml, 19.7 mmol) and N,N,N',N'-tetramethyl-1,6-diaminohexane (0.57 ml, 2.64 mmol) were added, and the mixture was cooled in an
25 ice-bath. p-Toluenesulfonyl chloride (2.75 g, 14.4 mmol) was added to this mixture, which was allowed to return to room temperature and stirred overnight. Water was poured into the reaction mixture, and the

mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica
5 gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(toluene-4-sulfonyloxy)piperidine-1-carboxylate (4.16 g, yield 89%) as a pale yellow powder.

¹H-NMR (CDCl₃) δppm:

10 1.44 (9H, s), 1.64 - 1.82 (4H, m), 2.44 (3H, s), 3.19 - 3.30 (2H, m), 3.54 - 3.64 (2H, m), 4.63 - 4.72 (1H, m), 7.31 - 7.37 (2H, m), 7.78 - 7.82 (2H, m).

Reference Example 138

Preparation of tert-butyl 4-(4-trifluoromethoxyphenylsulfanyl)piperidine-1-carboxylate
15 4-(Trifluoromethoxy)thiophenol (2.0 g, 10.3 mmol) was dissolved in THF (30 ml), and this solution was cooled in an ice-bath. To which sodium hydride (453 mg, 11.3 mmol) was added, and the mixture was
20 stirred for 30 minutes. To which tert-butyl 4-(toluene-4-sulfonyloxy)piperidine-1-carboxylate (3.66 g, 10.3 mmol) prepared in Reference Example 137 was added, and the resulting mixture was stirred at room temperature for 30 minutes, and then heated under
25 reflux for 1 hour. Water was added to the reaction mixture, and the mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate, and then filtered, and the filtrate was

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl chloride = 20/1) to afford tert-butyl 4-(4-trifluoromethoxyphenylsulfanyl)piperidine-1-carboxylate (3.12 g, yield 80%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.45 (9H, s), 1.46 - 1.60 (2H, m), 1.87 - 1.95 (2H, m), 2.86 - 2.98 (2H, m), 3.14 - 3.23 (1H, m), 3.94 - 4.00 (2H, m), 7.13 - 7.17 (2H, m), 7.40 - 7.47 (2H, m).

10 Reference Example 139

Preparation of 4-(4-trifluoromethoxyphenylsulfanyl)-piperidine

Using tert-butyl 4-(4-trifluoromethoxyphenylsulfanyl)piperidine-1-carboxylate prepared in Reference Example 138, 4-(4-trifluoromethoxyphenylsulfanyl)piperidine (yield 92%) as a colorless oil was prepared in the same manner as described in Reference Example 134.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.43 - 1.59 (2H, m), 1.91 - 1.98 (2H, m), 2.59 - 2.70 (2H, m), 3.06 - 3.20 (3H, m), 7.12 - 7.16 (2H, m), 7.40 - 7.46 (2H, m).

Reference Example 140

Preparation of tert-butyl 4-(4-trifluoromethoxybenzyl)-piperidine-1-carboxylate

Triphenyl-(4-trifluoromethoxybenzyl)-phosphonium bromide (2.0 g, 3.87 mmol) was dissolved in DMSO (20 ml), to which sodium hydride (168 mg, 4.2

mmol) was added, and the mixture was stirred for 30 minutes. Tert-butyl 4-oxopiperidine-1-carboxylate (700 mg, 3.51 mmol) was added to the mixture, and the resulting mixture was stirred at 60°C for 2 hours. The
5 reaction mixture was poured into water, and extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford
10 a colorless crystalline powder.

A mixture of this intermediate and a catalytic amount of 10% Pd/C in methanol (30 ml) was stirred at room temperature under an atmospheric
15 pressure of hydrogen for 3 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford tert-butyl 4-(4-trifluoromethoxybenzyl)piperidine-1-carboxylate (1.28 g, yield 60%) as a colorless oil.

20 ¹H-NMR (CDCl₃) δppm:
1.06 - 1.21 (2H, m), 1.45 (9H, s), 1.57 - 1.70 (3H, m),
2.52 - 2.69 (4H, m), 4.08 (2H, br), 7.09 - 7.17 (4H, m).

Reference Example 141

25 Preparation of 4-(4-trifluoromethoxybenzyl)piperidine

Using tert-butyl 4-(4-trifluoromethoxybenzyl)piperidine-1-carboxylate prepared in Reference Example 140, 4-(4-trifluoromethoxybenzyl)piperidine was

prepared in the same manner as described in Reference Example 134.

Colorless solid, yield 99%

^1H -NMR (CDCl_3) δ ppm:

5 1.06 - 1.22 (2H, m), 1.50 (1H, s), 1.53 - 1.68 (3H, m),
2.48 - 2.60 (4H, m), 3.02 - 3.08 (2H, m), 7.09 - 7.17
(4H, m).

Reference Example 142

Preparation of 1-benzyl-4-(4-trifluoromethoxy-
10 benzylidene)piperidine

Triphenyl-(4-trifluoromethoxybenzyl)
phosphonium bromide (21.6 g, 41.75 mmol) was dissolved
in DMSO (110 ml), to which sodium hydride (1.82 g,
45.52 mmol) was added, and the mixture was stirred for
15 30 minutes. 1-Benzyl-4-piperidone (7.18 g, 37.96 mmol)
was added to the mixture, and the resulting mixture was
stirred at 60°C for 2 hours. The reaction mixture was
poured into ice water, and extracted with ethyl
acetate. The extract was washed with brine, dried over
20 magnesium sulfate, and then filtered. The filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (methylene
chloride/ethyl acetate = 10/1) to afford 1-benzyl-4-(4-
trifluoromethoxybenzylidene)piperidine (9.75 g, yield
25 74%) as a yellow oil.

^1H -NMR (CDCl_3) δ ppm:

2.36 - 2.55 (8H, m), 3.53 (2H, s), 6.23 (1H, s), 7.11 -
7.34 (9H, m).

Using a corresponding starting material, a compound of Reference Example 143 was prepared in the same manner as described in Reference Example 142.

Reference Example 143

5 1-benzyl-4-(4-trifluoromethylbenzylidene)piperidine
a yellow oil, yield 52%

¹H-NMR (CDCl₃) δppm:

2.38 - 2.57 (8H, m), 3.53 (2H, s), 6.28 (1H, m), 7.24 -
7.56 (9H, m).

10 Reference Example 144

Preparation of 4-(4-trifluoromethoxybenzyl)piperidine
(an alternative method for synthesis of the compound in
Reference Example 141)

A mixture of 1-benzyl-4-(4-
15 trifluoromethylbenzylidene)piperidine (9.7 g, 27.92
mmol) prepared in Reference Example 142, 6 N
hydrochloric acid (9.3 ml), and 10% palladium/carbon
(970 mg) in ethanol (100 ml) was stirred at 50°C under
an atmospheric pressure of hydrogen for 5 hours. The
20 reaction mixture was filtered through Celite, and the
filtrate was concentrated under reduced pressure.
Water and 10% sodium hydroxide aqueous solution were
added to the residue, and the mixture was extracted
with methylene chloride. The extract was washed with
25 brine, dried over magnesium sulfate, and then filtered.
The filtrate was concentrated under reduced pressure to
afford 4-(4-trifluoromethoxybenzyl)piperidine (6.77 g,
yield 94%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.06 - 1.22 (2H, m), 1.50 (1H, s), 1.53 - 1.68 (3H, m),
2.48 - 2.60 (4H, m), 3.02 - 3.08 (2H, m), 7.09 - 7.17
(4H, m).

5 Using corresponding starting materials,
compounds of Reference Examples 145 and 146 were
prepared in the same manner as described in Reference
Example 144.

Reference Example 145

10 4-(4-trifluoromethylbenzyl)piperidine
a colorless crystalline powder, yield 94%

¹H-NMR (CDCl₃) δppm:

1.06 - 1.29 (2H, m), 1.50 - 1.69 (4H, m), 2.48 - 2.60
(4H, m), 3.02 - 3.09 (2H, m), 7.23 - 7.29 (2H, m), 7.51
15 - 7.54 (2H, m).

Reference Example 146

4-(4-chlorobenzyl)piperidine
a colorless crystalline powder, yield 94%

¹H-NMR (CDCl₃) δppm:

20 1.07 - 1.21 (2H, m), 1.53 - 1.82 (4H, m), 2.47 - 2.59
(4H, m), 3.02 - 3.08 (2H, m), 7.04 - 7.08 (2H, m), 7.22
- 7.27 (2H, m).

Reference Example 147

Preparation of 1-benzylpiperidine-4-carboxylic acid N-
25 methyl-N-methoxyamide

1-benzylpiperidine-4-carboxylic acid
hydrochloride (21 g, 82.3 mmol) was suspended in
chloroform, to which DMF (1 ml) and thionyl chloride

(30 ml) were added at room temperature, and the mixture was heated under reflux for 2 hours. The mixture was concentrated under reduced pressure to prepare an acid chloride compound.

5 In another vessel, N,O-dimethylhydroxylamine hydrochloride (12 g, 0.12 mol) was dissolved in acetone (200 ml)-water (20 ml), to which potassium carbonate (34.12 g, 246.9 mmol) was added, and the mixture was stirred while cooling in an ice-bath. A solution of
10 the previously prepared acid chloride compound in acetone (120 ml) was added dropwise to this mixture, which was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, to which water was added, and the mixture was
15 extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 1-benzylpiperidine-4-carboxylic acid N-methyl-N-methoxyamide (16.8 g, yield
20 78%) as a brown oil.

¹H-NMR (CDCl₃) δppm:

1.65 - 1.92 (4H, m), 1.97 - 2.07 (2H, m), 2.62 - 2.68 (1H, m), 2.91 - 2.96 (2H, m), 3.17 (3H, s), 3.51 (2H, s), 3.69 (3H, s), 7.20 - 7.32 (5H, m).

25 Reference Example 148

Preparation of 1-benzyl-4-(4-trifluoromethoxybenzoyl)-piperidine

1-Bromo-4-trifluoromethoxybenzene (5.3 g,

22.0 mmol) was dissolved in dry THF (70 ml) under a nitrogen atmosphere, and this solution was cooled to -60°C. n-Butyllithium (1.6 M) hexane solution (15 ml, 24.0 mmol) was added dropwise to the solution, and the mixture was allowed to reach a temperature of -30°C and stirred for 1 hour. This mixture was cooled to -60°C again, to which a solution of 1-benzylpiperidine-4-carboxylic acid N-methyl-N-methoxyamide (4.1 g, 15.6 mmol) prepared in Reference Example 147 in THF (10 ml) was added dropwise, and the mixture was stirred for 1 hour and then at 0°C for 3 hours. The reaction mixture was poured into saturated ammonium chloride aqueous solution, and extracted with diethyl ether. The extract was washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford 1-benzyl-4-(4-trifluoromethoxybenzoyl)piperidine (4.8 g, yield 85%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.80 - 1.89 (4H, m), 2.04 - 2.18 (2H, m), 2.94 - 3.01 (2H, m), 3.15 - 3.24 (1H, m), 3.55 (2H, s), 7.19 - 7.34 (7H, m), 7.95 - 8.01 (2H, m).

Using a corresponding starting material, a compound of Reference Example 149 was prepared in the same manner as described in Reference Example 148.

Reference Example 149

1-benzyl-4-(4-trifluoromethylbenzoyl)piperidine

a pale yellow oil, yield 66%

¹H-NMR (CDCl₃) δppm:

1.78 - 1.89 (4H, m), 2.09 - 2.19 (2H, m), 2.94 - 3.02
5 (2H, m), 3.16 - 3.29 (1H, m), 3.55 (2H, m), 7.26 - 7.34
(5H, m), 7.70 - 7.74 (2H, m), 8.00 - 8.04 (2H, m).

Reference Example 150

Preparation of 4-(4-trifluoromethoxybenzoyl)piperidine

1-Benzyl-4-(4-trifluoromethoxybenzoyl)-

10 piperidine (4.8 g, 13.22 mmol) prepared in Reference
Example 148 was dissolved in methylene chloride (60
ml), and this solution was cooled in an ice-bath. 2-
Chloroethyl chloroformate (2.9 ml, 26.4 mmol) was added
dropwise to the solution, and the mixture was stirred
15 at the same temperature for 30 minutes. The reaction
mixture was concentrated under reduced pressure,
methanol (100 ml) was added to the residue, and the
resulting mixture was heated under reflux for 15
minutes. Water was added to the reaction mixture,
20 which was stirred for 30 minutes, and neutralized with
sodium hydroxide aqueous solution. The mixture was
extracted with methylene chloride. The extract was
washed with brine, dried over magnesium sulfate, and
then filtered. The filtrate was concentrated under
25 reduced pressure, and the residue was purified by
silica gel column chromatography (n-hexane/ethyl acetate
= 1/1) to afford 4-(4-trifluoromethoxybenzoyl)-
piperidine (1.3 g, yield 36%) as a pale orange-colored

crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.57 - 1.88 (5H, m), 2.71 - 2.81 (2H, m), 3.15 - 3.23
(2H, m), 3.29 - 3.42 (1H, m), 7.27 - 7.28 (2H, m), 7.95
5 - 8.05 (2H, m).

Using corresponding starting materials,
compounds of Reference Examples 151 and 152 were
prepared in the same manner as described in Reference
Example 150.

10 Reference Example 151

4-(4-trifluoromethylbenzoyl)piperidine

a colorless crystalline powder, yield 68%

¹H-NMR (CDCl₃) δppm:

1.61 - 1.76 (3H, m), 1.82 - 1.89 (2H, m), 2.72 - 2.83
15 (2H, m), 3.16 - 3.24 (2H, m), 3.32 - 3.44 (1H, m), 7.72
- 7.76 (2H, m), 8.01 - 8.05 (2H, m).

Reference Example 152

4-(4-chlorobenzoyl)piperidine

a colorless crystalline powder, yield 100%

20 ¹H-NMR (CDCl₃) δppm:

1.60 - 1.84 (5H, m), 2.72 - 2.83 (2H, m), 3.16 - 3.24
(2H, m), 3.30 - 3.40 (1H, m), 7.41 - 7.47 (2H, m), 7.85
- 7.91 (2H, m).

Reference Example 153

25 Preparation of N-{2-[4-(4-trifluoromethylphenyl)-
piperazin-1-yl]ethyl}phthalimide

A mixture of 1-(4-trifluoromethylphenyl)-
piperazine (5.2 g, 22.59 mmol), N-(2-bromoethyl)-

phthalimide (5.22 g, 20.53 mmol) and potassium carbonate (3.36 g, 24.28 mmol) in DMF (30 ml) was stirred at 100°C for 2 hours. The reaction mixture was allowed to return to room temperature, to which water
5 was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene
10 chloride/ethyl acetate = 50/1), and the resulting solid was washed with methanol, and then dried *in vacuo* to afford N-{2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl} phthalimide (4.85 g, yield 53%) as a white powder.

15 ¹H-NMR (CDCl₃) δppm:

2.64 - 2.72 (6H, m), 3.18 - 3.23 (4H, m), 3.86 (2H, t, J = 6.4 Hz), 6.89 (2H, d, J = 8.7 Hz), 7.45 (2H, d, J = 8.7 Hz), 7.70 - 7.75 (2H, m), 7.81 - 7.86 (2H, m).

Reference Example 154

20 Preparation of 2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethylamine

N-{2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl}phthalimide (4 g, 9.92 mmol) prepared in Reference Example 153 was suspended in ethanol (30 ml),
25 to which hydrazine monohydrate (0.53 ml, 10.91 mmol) was added, and the mixture was heated under reflux for 5 hours. The reaction mixture was allowed to return to room temperature, and the resulting precipitates were

collected by filtration. This was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 100/1) to afford 2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethylamine (2.87 g, yield 5 100%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.33 (2H, bs), 2.49 (2H, t, J = 6.1 Hz), 2.59 - 2.63 (4H, m), 2.84 (2H, t, J = 6.1 Hz), 3.26 - 3.31 (4H, m), 6.92 (2H, d, J = 8.7 Hz), 7.48 (2H, d, J = 8.7 Hz).

10 Reference Example 155

Preparation of N-{2-[4-(4-trifluoromethylphenyl)-piperazin-1-yl]ethyl}formamide

A mixture of 2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethylamine (906 mg, 3.32 mmol) prepared 15 in Reference Example 154 and ethyl formate (10 ml) was heated under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to 20 afford N-{2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl} formamide (942 mg, yield 94%) as a white powder.

¹H-NMR (CDCl₃) δppm:

2.53 - 2.65 (6H, m), 3.26 - 3.31 (4H, m), 3.42 - 3.49 25 (2H, m), 6.05 (1H, bs), 6.92 (2H, d, J = 8.7 Hz), 7.49 (2H, d, J = 8.7 Hz), 8.21 (1H, s).

Reference Example 156

Preparation of N-methyl-{2-[4-(4-trifluoromethyl-

phenyl)piperazin-1-yl]ethyl} amine

Lithium aluminum hydride (237 mg, 6.25 mmol) was suspended in THF (20 ml), which was stirred while cooling in an ice-bath. To which a solution of N-{2-
5 [4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl}-formamide (942 mg, 3.13 mmol) prepared in Reference Example 155 in THF (10 ml) was added dropwise, and the mixture was stirred at room temperature for 2 hours and then heated under reflux for 2 hours. The reaction
10 mixture was allowed to return to room temperature, to which water and a 15% sodium hydroxide aqueous solution were added carefully. To the mixture, sodium sulfate was added, and the resulting mixture was vigorously stirred and filtered through Celite. The filtrate was
15 concentrated under reduced pressure to afford N-methyl-{2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl}-amine (900 mg, yield 100%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

2.47 (3H, s), 2.52 - 2.74 (8H, m), 3.26 - 3.30 (4H, m),
20 3.71 - 3.77 (1H, m), 6.91 (2H, d, J = 8.7 Hz), 7.47
(2H, d, J = 8.7 Hz).

Reference Example 157

Preparation of tert-butyl 4-(2-methylaminoethyl)-
piperazine-1-carboxylate

25 Tert-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (3.13 g, 12.58 mmol) was dissolved in methanol (20 ml), to which 40% methylamine methanol solution (30 ml) was added, and the mixture was heated

- under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride. The mixture was washed with saturated sodium hydrogencarbonate aqueous solution. The organic layer was dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure to afford tert-butyl 4-(2-methylaminoethyl)piperazine-1-carboxylate (3.0 g, yield 98%) as a pale yellow oil.
- 5 ¹H-NMR (CDCl₃) δppm:
1.46 (9H, m), 1.66 (1H, s), 2.36 - 2.41 (4H, m), 2.45 (3H, s), 2.46 - 2.53 (2H, m), 2.65 - 2.70 (2H, m), 3.40 - 3.44 (4H, m).

Reference Example 158

- 15 Preparation of N-[2-(4-trifluoromethylphenoxy)ethyl]-phthalimide

- A mixture of N-(2-hydroxyethyl)phthalimide (3.59 g, 18.75 mmol), 4-hydroxybenzotrifluoride (3.04 g, 18.75 mmol), diethyl azodicarboxylate (4.37 ml, 28.13 mmol) and triphenylphosphine (7.38 g, 28.13 mmol) in THF (50 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 5/1) to afford N-[2-(4-trifluoromethylphenoxy)ethyl]phthalimide (4.05 g, yield 69%) as a colorless crystalline powder.
- 25 ¹H-NMR (CDCl₃) δppm:

4.11 - 4.16 (2H, m), 4.25 - 4.30 (2H, m), 6.92 - 6.96 (2H, m), 7.48 - 7.52 (2H, m), 7.72 - 7.77 (2H, m), 7.83 - 7.89 (2H, m).

Reference Example 159

5 Preparation of 2-(4-trifluoromethylphenoxy)ethylamine

Using N-[2-(4-trifluoromethylphenoxy)ethyl]-phthalimide prepared in Reference Example 158, 2-(4-trifluoromethylphenoxy) ethylamine was prepared in the same manner as described in Reference Example 154.

10 a colorless oil, yield 95%

^1H -NMR (CDCl_3) δ ppm:

1.36 (2H, s), 3.11 (2H, t, $J = 5.1$ Hz), 4.03 (2H, t, $J = 5.1$ Hz), 6.97 (2H, d, $J = 8.6$ Hz), 7.54 (2H, d, $J = 8.6$ Hz).

15 Reference Example 160

Preparation of N-[2-(4-trifluoromethylphenoxy)ethyl]-formamide

A mixture of 2-(4-trifluoromethylphenoxy) ethylamine (1.38 g, 6.72 mmol) prepared in Reference
20 Example 159 and ethyl formate (10 ml) was heated under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford N-[2-
25 (4-trifluoromethylphenoxy)ethyl]formamide (1.51 g, yield 97%) as a white powder.

^1H -NMR (CDCl_3) δ ppm:

3.72 - 3.78 (2H, m), 4.09 - 4.13 (2H, m), 6.02 (1H,

bs), 6.96 (2H, d, $J = 8.6$ Hz), 7.56 (2H, d, $J = 8.6$ Hz), 8.24 (1H, s).

Reference Example 161

Preparation of N-methyl-N-[2-(4-

5 trifluoromethylphenoxy)ethyl]amine

N-[2-(4-trifluoromethylphenoxy)ethyl]-
formamide (2.02 g, 8.66 mmol) prepared in Reference
Example 160 was dissolved in THF (20 ml). Borane-THF
complex (1 M) THF solution (21.7 ml, 21.7 mmol) was
10 added dropwise to this solution while cooling in an
ice-bath, and the mixture was stirred overnight. The
reaction mixture was cooled, to which water and 6N
hydrochloric acid were added, and the mixture was
stirred for 20 minutes. The reaction mixture was
15 neutralized with a sodium hydroxide aqueous solution,
and the mixture extracted with methylene chloride. The
extract was dried over magnesium sulfate, and then
filtered. The filtrate was concentrated under reduced
pressure. The residue was purified by silica gel
20 column chromatography (methylene chloride/ methanol =
200/1) to afford N-methyl-N-[2-(4-
trifluoromethylphenoxy)ethyl]amine (1.05 g, yield 55%)
as a white powder.

^1H -NMR (CDCl_3) δ ppm:

25 2.68 (3H, d, $J = 5.8$ Hz), 3.05 - 3.28 (2H, m), 4.06
(1H, br), 4.10 - 4.18 (1H, m), 4.45 - 4.54 (1H, m),
6.98 (2H, d, $J = 8.5$ Hz), 7.58 (2H, d, $J = 8.5$ Hz).

Reference Example 162

Preparation of N-methyl-N-[2-(4-trifluoromethoxy-
phenoxy)ethyl]amine

1-(2-Bromoethoxy)-4-(trifluoromethoxy)benzene
(2.2 g, 7.72 mmol) was dissolved in methanol (20 ml),
5 to which 40% methylamine methanol solution (20 ml) was
added, and the mixture was heated under reflux for 5
hours. The reaction mixture was concentrated under
reduced pressure, and the residue was dissolved in
methylene chloride, and the mixture was washed with
10 saturated sodium hydrogencarbonate aqueous solution.
The organic layer was dried over magnesium sulfate, and
filtered, and the filtrate was concentrated under
reduced pressure to afford N-methyl-N-[2-(4-
trifluoromethoxyphenoxy)ethyl]amine (1.44 g, yield 79%)
15 as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.54 (1H, s), 2.51 (3H, s), 2.97 (2H, t, $J = 5.1$ Hz),
4.06 (2H, t, $J = 5.1$ Hz), 6.85 - 6.92 (2H, m), 7.10 -
7.17 (2H, m).

20 Reference Example 163

Preparation of N-methyl-N-[2-(4-
trifluoromethylphenoxy)ethyl]amine

Using 1-(2-bromoethoxy)-4-(trifluoromethyl)-
benzene, N-methyl-N-[2-(4-trifluoromethylphenoxy)-
25 ethyl]amine was prepared in the same manner as
described in Reference Example 162.

a white powder, yield 82%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.68 (3H, d, $J = 5.8$ Hz), 3.02 - 3.28 (2H, m), 3.92 - 4.18 (2H, m), 4.41 - 4.54 (1H, m), 6.98 (2H, d, $J = 8.5$ Hz), 7.58 (2H, d, $J = 8.5$ Hz)

Reference Example 164

5 Preparation of N,N'-dimethyl-N-[4-(trifluoromethyl)-phenyl]-1,2-ethylenediamine

A mixture of 4-bromobenzotrifluoride (3.0 g, 13.3 mmol), N,N'-dimethylethylenediamine (9.4 g, 0.11 mol), palladium acetate (60 mg, 0.27 mmol), BINAP (250 mg, 0.40 mmol) and sodium tert-butoxide (1.80 g, 18.7 mmol) in toluene (20 ml) was refluxed under a nitrogen atmosphere for 3 hours. Ethyl acetate and water were added to the reaction mixture, and the mixture was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford N,N'-dimethyl-N-[4-(trifluoromethyl)phenyl]-1,2-ethylenediamine (650 mg, yield 21%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

25 1.53 (1H, s), 2.47 (3H, s), 2.82 (2H, t, $J = 6.7$ Hz), 3.02 (3H, s), 3.52 (2H, t, $J = 6.7$ Hz), 6.74 (2H, d, $J = 8.8$ Hz), 7.43 (2H, d, $J = 8.8$ Hz).

Reference Example 165

Preparation of tert-butyl N-[1-(4-chlorophenyl)-
piperidin-4-yl]-N-methylcarbamate

A mixture of p-bromochlorobenzene (3.13 g, 16.3 mmol), tert-butyl (piperidin-4-yl)-N-methylcarbamate (3.5 g, 10.8 mmol), palladium acetate (73 mg, 0.33 mmol), (S)-(-)-BINAP (305 mg, 0.49 mmol) and sodium tert-butoxide (2.2 g, 22.9 mmol) in toluene (30 ml) was refluxed under a nitrogen atmosphere for 3 hours. Ethyl acetate and water were added to the reaction mixture, the mixture was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) to afford tert-butyl N-[1-(4-chlorophenyl)piperidin-4-yl]-N-methylcarbamate (4.7 g, yield 89%) as a yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.47 (9H, s), 1.70 - 1.90 (4H, m), 2.73 - 2.82 (2H, m), 2.74 (3H, s), 3.64 - 3.71 (2H, m), 4.08 (1H, br), 6.81 - 6.87 (2H, m), 7.15 - 7.22 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 166 to 168 were prepared in the same manner as described in Reference Example 165.

Reference Example 166

tert-butyl N-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]-N-methylcarbamate

yield 88%

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.48 (9H, s), 1.72 - 1.91 (4H, m), 2.76 (3H, s), 2.79 - 2.85 (2H, m), 3.67 - 3.73 (2H, m), 4.10 (1H, br), 6.86 - 6.93 (2H, m), 7.07 - 7.11 (2H, m).

Reference Example 167

10 tert-butyl N-[1-(4-trifluoromethylphenyl)piperidin-4-yl]-N-methylcarbamate

yield 91%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.47 (9H, s), 1.72 - 1.87 (4H, m), 2.74 (3H, s), 2.82 - 15 2.94 (2H, m), 3.83 - 3.89 (2H, m), 4.12 (1H, br), 6.92 (2H, d, $J = 8.7$ Hz), 7.46 (2H, d, $J = 8.7$ Hz).

Reference Example 168

tert-butyl N-[1-(4-cyanophenyl)piperidin-4-yl]-N-methylcarbamate

20 yield 73%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.47 (9H, s), 1.69 - 1.77 (4H, m), 2.73 (3H, s), 2.87 - 3.00 (2H, m), 3.89 - 3.97 (2H, m), 4.16 (1H, br), 6.84 - 6.89 (2H, m), 7.45 - 7.51 (2H, m).

25 Reference Example 169

Preparation of N-[1-(4-chlorophenyl)piperidin-4-yl]-N-methylamine

Tert-butyl N-[1-(4-chlorophenyl)piperidin-4-

yl]-N-methylcarbamate (4.71 g, 14.5 mmol) prepared in Reference Example 165 was dissolved in methylene chloride (30 ml), to which trifluoroacetic acid (20 ml) was added dropwise, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was then dissolved in methylene chloride. The solution was neutralized with sodium hydroxide aqueous solution, and the mixture was extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford N-[1-(4-chlorophenyl)piperidin-4-yl]-N-methylamine (3.1 g, yield 95%) as a pale brown oil.

¹H-NMR (CDCl₃) δppm:

0.99 (1H, s), 1.38 - 1.54 (2H, m), 1.95 - 2.00 (2H, m), 2.44 - 2.54 (1H, m), 2.46 (3H, s), 2.71 - 2.82 (2H, m), 3.55 - 3.63 (2H, m), 6.81 - 6.87 (2H, m), 7.14 - 7.21 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 170 to 172 were prepared in the same manner as described in Reference Example 169.

Reference Example 170

N-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]-N-methylamine

a pale brown powder, yield 100%

¹H-NMR (CDCl₃) δppm:

0.96 (1H, s), 1.39 - 1.55 (2H, m), 1.96 - 2.02 (2H, m),
 2.44 - 2.57 (1H, m), 2.47 (3H, s), 2.73 - 2.84 (2H, m),
 3.58 - 3.66 (2H, m), 6.86 - 6.92 (2H, m), 7.05 - 7.10
 (2H, m).

5 Reference Example 171

N-[1-(4-trifluoromethylphenyl)piperidin-4-yl]-N-
 methylamine

a pale brown powder, yield 100%

¹H-NMR (CDCl₃) δppm:

10 0.96 (1H, s), 1.36 - 1.52 (2H, m), 1.96 - 2.02 (2H, m),
 2.47 (3H, s), 2.50 - 2.62 (1H, m), 2.82 - 2.94 (2H, m),
 3.72 - 3.80 (2H, m), 6.92 (2H, d, J = 8.8 Hz), 7.45
 (2H, d, J = 8.8 Hz).

Reference Example 172

15 N-[1-(4-cyanophenyl)piperidin-4-yl]-N-methylamine

a pale brown powder, yield 99%

¹H-NMR (CDCl₃) δppm:

1.05 (1H, s), 1.34 - 1.49 (2H, m), 1.95 - 2.02 (2H, m),
 2.47 (3H, s), 2.55 - 2.67 (1H, m), 2.90 - 3.01 (2H, m),
 20 3.76 - 3.84 (2H, m), 6.82 - 6.90 (2H, m), 7.43 - 7.50
 (2H, m).

Reference Example 173

Preparation of benzyl N-(2-methyl-2-propenyl)carbamate

2-Methallylamine hydrochloride (21.52 g, 0.2
 25 mol) was dissolved in water (200 ml), to which benzyl
 chloroformate (37.53 g, 0.22 mol) was added, and the
 mixture was cooled in an ice-bath. Sodium carbonate
 (46.63 g, 0.44 mol) was gradually added to this

mixture, which was stirred at room temperature for 3 hours. After the reaction mixture was extracted with methylene chloride twice, the extracts were combined, dried over sodium sulfate, and then filtered, and the
5 filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 7/1) to afford benzyl N-(2-methyl-2-propenyl)carbamate (41.58 g, quantitative) as a colorless oil.

10 ^1H -NMR (CDCl_3) δ ppm:

1.74 (3H, s), 3.75 (2H, d, $J = 6.2$ Hz), 4.69 - 4.94 (2H, m), 5.13 (2H, s), 7.26 - 7.39 (5H, m).

Reference Example 174

Production of 4-chlorobenzyl N-(2-methyl-2-propenyl)-
15 carbamate

4-chlorobenzyl alcohol (3.00 g, 21.0 mmol) and triphosgene (3.12 g, 10.5 mmol) were dissolved in toluene (15 ml), to which N-ethyldiisopropylamine (3.6 ml, 21.0 mmol) was added while cooling in an ice-bath,
20 and the mixture was stirred for 1 hour. The reaction mixture was poured into water, and extracted with methylene chloride twice. The extracts were combined and dried over magnesium sulfate, and then filtered. The filtrate was concentrated under a reduced pressure.
25 A solution of 2-methallylamine hydrochloride (2.49 g, 23.1 mmol) in water (40 ml) were added to the residue, to which sodium carbonate (5.15 g, 48.6 mmol) was added under while cooling in an ice-bath, and the mixture was

stirred for 15 minutes. The reaction mixture was extracted with methylene chloride twice, and the extracts were combined, dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 10/1) to afford 4-chlorobenzyl N-(2-methyl-2-propenyl)carbamate (4.06 g, yield 80%) as a colorless liquid.

¹H-NMR (CDCl₃) δppm:

1.74 (3H, s), 3.74 (2H, d, J = 5.8 Hz), 4.73 - 4.91 (2H, m), 5.08 (2H, s), 7.26 - 7.41 (4H, m).

Reference Example 175

Preparation of 4-fluorobenzyl N-(2-methyl-2-propenyl)-carbamate

4-Fluorobenzyl alcohol (3.00 g, 23.8 mmol) was dissolved in THF (60 ml), to which 1,1'-carbonyldiimidazole (4.05 g, 25.0 mmol) was added while cooling in an ice-bath, and the mixture was stirred for 30 minutes. 2-Methallylamine hydrochloride (2.81 g, 26.2 mmol) and triethylamine (3.98 g, 28.5 mmol) were added to the mixture, which was stirred for 2 hours. After the reaction mixture was concentrated under reduced pressure, water were added to the residue, and the mixture was extracted with methylene chloride twice. The extracts were combined, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (n-hexane/ethyl acetate = 10/1) to afford 4-fluorobenzyl N-(2-methyl-2-propenyl)carbamate (4.69 g, yield 88%) as a colorless oil.

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.73 (3H, s), 3.74 (2H, d, $J = 5.8$ Hz), 4.55 - 4.95 (3H, m), 5.08 (2H, s), 6.95 - 7.14 (2H, m), 7.27 - 7.41 (2H, m).

Reference Example 176

10 Preparation of 3-methoxymethoxy-2-methyl-1-propene

Chloromethyl methyl ether (105 ml, 1386 mmol) and N-ethyldiisopropylamine (265 ml, 1525 mmol) were added to a solution of 2-methyl-2-propen-1-ol (50 g, 693 mmol) in THF (500 ml) while cooling in an ice-bath, 15 and the mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered and washed with diethyl ether, and the filtrate was concentrated under a reduced pressure. The residue was dissolved in diethyl ether, washed with water, a saturated sodium 20 hydrogencarbonate solution and then water, dried over magnesium sulfate. After filtration, the filtrate was concentrated under a reduced pressure to afford 3-methoxymethoxy-2-methylpropene (9.7 g, yield 12%) as colorless liquid.

25 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.76 (3H, s), 3.39 (3H, s), 3.97 (2H, s), 4.65 (2H, s), 4.85 - 4.94 (1H, m), 4.98 - 5.06 (1H, m).

Reference Example 177

Preparation of 2-methoxymethoxymethyl-2-methyloxirane

m-Chloroperbenzoic acid (22.7 g, 92 mmol) was gradually added to a solution of 3-methoxymethoxy-2-methyl-1-propene (9.7 g, 84 mmol) prepared in Reference Example 176 in methylene chloride (200 ml) while cooling in an ice-bath and the mixture was stirred at room temperature for 6 hours. Sodium hydrogencarbonate (14.1 g, 168 mmol), water and methylene chloride were added to the reaction mixture, which was stirred for a while. The organic layer was separated, washed with sodium hydrogencarbonate aqueous solution, sodium thiosulfate aqueous solution and then sodium hydrogencarbonate aqueous solution, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 2-methoxymethoxymethyl-2-methyloxirane (6.8 g, yield 62%) as a green-colored oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.40 (3H, s), 2.65 (1H, d, $J = 4.9$ Hz), 2.78 (1H, d, $J = 4.9$ Hz), 3.38 (3H, s), 3.53 (1H, d, $J = 11.1$ Hz), 3.62 (1H, d, $J = 11.1$ Hz), 4.65 (2H, s).

Reference Example 178

Preparation of tert-butyl 4-(4-chlorobenzyl)piperazine-1-carboxylate

Potassium carbonate (1.45 g, 10.47 mmol) and 4-chlorobenzyl chloride (1.82 g, 8.86 mmol) were added to a solution of tert-butyl piperazine-1-carboxylate (1.5 g, 8.05 mmol) in DMF (10 ml), and the mixture was

stirred at 50°C for 1 hour. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with water, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford tert-butyl 4-(4-chlorobenzyl)piperazine-1-carboxylate (2.50 g, quantitative) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.45 (9H, s), 2.36 (4H, t, J = 5.0 Hz), 3.42 (4H, t, J = 5.0 Hz), 3.46 (2H, s), 7.23 - 7.31 (4H, m).

Reference Example 179

Preparation of 1-(4-chlorobenzyl)piperazine

Trifluoroacetic acid (8 ml) was added to a solution of tert-butyl 4-(4-chlorobenzyl)piperazine-1-carboxylate (2.50 g, 8.05 mmol) prepared in Reference Example 178 in methylene chloride (16 ml), and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. Sodium hydroxide aqueous solution was added to the residue, and the mixture was extracted with methylene chloride. The extract was dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 1-(4-chlorobenzyl)piperazine (1.70 g, quantitative) as a colorless oil.

¹H-NMR (DMSO-d₆) δppm:

2.55 - 2.74 (4H, m), 3.57 - 3.76 (6H, m), 7.35 - 7.45 (4H, m), 8.55 - 8.88 (1H, br).

Reference Example 180

Preparation of 1-(4-trifluoromethylbenzyl)piperazine

5 Using tert-butyl 4-(4-trifluoromethylbenzyl)-piperazine-1-carboxylate, 1-(4-trifluoromethylbenzyl)-piperazine was prepared in the same manner as described in Reference Example 179.
yield 100%

10 ¹H-NMR (CDCl₃) δppm:

2.72 (4H, t, J = 4.9 Hz), 3.16 - 3.26 (4H, m), 3.62 (2H, s), 7.44 (2H, d, J = 8.1 Hz), 7.59 (2H, d, J = 8.1 Hz).

Reference Example 181

15 Preparation of 1-(4-trifluoromethoxybenzyl)piperazine

 Using tert-butyl 4-(4-trifluoromethoxybenzyl)piperazine-1-carboxylate, 1-(4-trifluoromethoxybenzyl)piperazine was prepared in the same manner as described in Reference Example 179.

20 yield 100%

¹H-NMR (CDCl₃) δppm:

2.70 (4H, t, J = 4.9 Hz), 3.19 (4H, t, J = 4.9 Hz), 3.56 (2H, s), 7.17 (2H, d, J = 7.9 Hz), 7.33 (2H, d, J = 7.9 Hz).

25 Reference Example 182

Preparation of 4-[4-(4-

trifluoromethoxybenzyl)piperazin-1-yl]phenol

4-(4-hydroxyphenyl)piperazine (3 g, 16.8

mmol) and 4-trifluoromethoxy benzaldehyde (3.36 g, 17.7 mmol) were dissolved in methanol (60 ml) and methylene chloride (15 ml). Sodium cyanoborohydride (1.59 g, 25.3 mmol) and acetic acid (1.6 ml) were added to this solution while cooling in an ice-bath, and the mixture was stirred for 2 hours. Saturated sodium hydrogen-carbonate aqueous solution and methylene chloride were added to the reaction mixture, which was extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford 4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenol (3.36 g, yield 57%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.59 - 2.64 (4H, m), 3.05 - 3.10 (4H, m), 3.56 (2H, s), 4.90 - 5.40 (1H, br), 6.69 - 6.75 (2H, m), 6.79 - 6.85 (2H, m), 7.16 (2H, d, $J = 8.4$ Hz), 7.37 (2H, d, $J = 8.4$ Hz).

Reference Example 183

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine

A mixture of 1-(4-trifluoromethoxyphenyl)-piperazine (4.4 g, 17.8 mmol), 2-(4-bromophenoxy)-tetrahydropyran (4.6 g, 17.8 mmol), palladium acetate (159 mg, 0.71 mmol), BINAP (666 mg, 1.07 mmol) and

sodium tert-butoxide (2.2 g, 23.1 mmol) in toluene (40 ml) was refluxed under a nitrogen atmosphere for 5 hours. Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine (2.7 g, yield 35%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.54 - 2.05 (6H, m), 3.21 - 3.34 (8H, m), 3.55 - 3.64 (1H, m), 3.89 - 3.99 (1H, m), 5.31 - 5.34 (1H, m), 6.90 - 7.03 (6H, m), 7.11 - 7.16 (2H, m).

This title compound was also prepared by the method described in Reference Example 185.

Reference Example 184

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-piperazine

A mixture of 2-(4-bromophenoxy)-tetrahydropyran (7.8 g, 30.3 mmol), piperazine (15.7 g, 180 mmol), palladium acetate (136 mg, 0.61 mmol), BINAP (567 mg, 0.91 mmol) and sodium tert-butoxide (3.8 g, 39.4 mmol) in toluene (50 ml) was refluxed under a

nitrogen atmosphere for 2 hours. Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate
5 was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl
10 acetate = 20/1) to afford 1-[4-(tetrahydropyran-2-yloxy)phenyl]piperazine (6.8 g, yield 85%) as a pale gray powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.57 - 2.04 (6H, m), 3.00 - 3.06 (8H, m), 3.53 - 3.66
15 (1H, m), 3.89 - 3.99 (1H, m), 5.29 - 5.32 (1H, m), 6.84 - 6.90 (2H, m), 6.95 - 7.02 (2H, m).

Reference Example 185

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine (an alternative
20 method for synthesis of the compound in Reference Example 183)

A mixture of 1-[4-(tetrahydropyran-2-yloxy)phenyl]piperazine (2.1 g, 8.05 mmol) prepared in Reference Example 184, 4-trifluoromethoxy-1-bromobenzene (1.9 g, 8.05 mmol), palladium acetate (72
25 mg, 0.32 mmol), BINAP (300 mg, 0.48 mmol) and sodium tert-butoxide (1.0 g, 10.5 mmol) in toluene (30 ml) was refluxed under a nitrogen atmosphere for 5 hours.

Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The
5 extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-[4-
10 (tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine (3.1 g, yield 90%) as a white powder.

Reference Example 186

Preparation of 4-[4-(4-
15 trifluoromethoxyphenyl)piperazin-1-yl]phenol

A mixture of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine (2.65 g, 6.27 mmol) prepared in Reference Example 185 and pyridinium p-toluene sulfonate (473 mg, 1.88 mmol)
20 in ethanol (50 ml) was stirred at 70°C for 5 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride and a saturated sodium hydrogencarbonate aqueous solution were added to the residue, which was stirred for a while. The mixture
25 was extracted with methylene chloride, and the extract was dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column

chromatography (methylene chloride/ethyl acetate = 10/1) to afford 4-[4-(4-trifluoromethoxyphenyl)-piperazin-1-yl]phenol (1.95 g, yield 92%) as a white powder.

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.19 - 3.24 (4H, m), 3.29 - 3.34 (4H, m), 4.50 (1H, s),
6.76 - 6.80 (2H, m), 6.87 - 6.97 (4H, m), 7.11 - 7.15
(2H, m).

Using corresponding starting materials,
10 compounds of Reference Examples 187 and 188 were
prepared in the same manner as described in Reference
Example 186.

Reference Example 187

4-[4-(4-trifluoromethylphenyl)piperazin-1-yl]phenol
15 a white powder, yield 82%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.18 - 3.23 (4H, m), 3.41 - 3.45 (4H, m), 4.47 (1H, s),
6.76 - 6.82 (2H, m), 6.87 - 7.00 (4H, m), 7.48 - 7.52
(2H, m).

20 Reference Example 188

4-[4-(4-chlorophenyl)piperazin-1-yl]phenol
a white powder, yield 23%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.18 - 3.23 (4H, m), 3.28 - 3.32 (4H, m), 4.45 (1H, s),
25 6.77 - 6.81 (2H, m), 6.87 - 6.92 (4H, m), 7.21 - 7.24
(2H, m).

Reference Example 189

Preparation of tert-butyl 4-(4-

trifluoromethoxyphenoxy)piperidine-1-carboxylate

Tert-butyl 4-hydroxypiperidine-1-carboxylate (56.5 g, 0.28 mol), 4-trifluoromethoxyphenol (50 g, 0.28 mol) and triphenylphosphine (108 g, 0.42 mol) were dissolved in THF (500 ml). Diethyl azodicarboxylate (65 ml, 0.42 mol) was added dropwise to this solution under reflux, and the mixture was refluxed for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 5/1) to afford tert-butyl 4-(4-trifluoromethoxyphenoxy)-piperidine-1-carboxylate (92 g, yield 91%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.47 (9H, s), 1.69 - 1.80 (2H, m), 1.85 - 1.96 (2H, m), 3.28 - 3.39 (2H, m), 3.64 - 3.75 (2H, m), 4.40 - 4.46 (1H, m), 6.85 - 6.92 (2H, m), 7.11 - 7.15 (2H, m).

Reference Example 190

Preparation of 4-(4-trifluoromethoxyphenoxy)piperidine

Tert-butyl 4-(4-trifluoromethoxyphenoxy)-piperidine-1-carboxylate (92 g, 254.59 mmol) prepared in Reference Example 189 was dissolved in methylene chloride (100 ml). Trifluoroacetic acid (200 ml) was added dropwise to this solution at room temperature, and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure, and the residue was then dissolved in methylene chloride, which was neutralized with a sodium hydroxide aqueous

solution. The mixture was extracted with methylene chloride. The extract was washed with brine, dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the
5 residue was then purified by silica gel column chromatography (methylene chloride/methanol = 5/1) to afford 4-(4-trifluoromethoxyphenoxy)piperidine (55 g, yield 83%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

10 1.65 - 1.78 (2H, m), 2.00 - 2.07 (2H, m), 2.73 - 2.83 (2H, m), 3.12 - 3.21 (2H, m), 4.32 - 4.38 (2H, m), 6.85 - 6.92 (2H, m), 7.10 - 7.15 (2H, m).

Reference Example 191

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-
15 (4-trifluoromethoxyphenoxy)piperidine

A mixture of 4-(4-trifluoromethoxyphenoxy)piperidine (30.3 g, 0.116 mol) prepared in Reference Example 190, 2-(4-bromophenoxy)tetrahydropyran (30 g, 0.116 mol), palladium acetate (1.0 g, 4.64 mmol), BINAP
20 (4.3 g, 6.96 mmol) and cesium carbonate (49 g, 0.151 mol) in toluene (300 ml) was refluxed under a nitrogen atmosphere for 30 hours. Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by
25 filtration through Celite, and the filtrate was then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced

pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenoxy)piperidine (32.6 g, yield 64%)
5 as a yellow powder.

¹H-NMR (CDCl₃) δppm:

1.55 - 1.75 (3H, m), 1.81 - 2.20 (7H, m), 2.95 - 3.04
(2H, m), 3.38 - 3.42 (2H, m), 3.55 - 3.66 (1H, m), 3.87
- 3.99 (1H, m), 4.36 - 4.45 (1H, m), 5.29 - 5.32 (1H,
10 m), 6.89 - 7.01 (6H, m), 7.11 - 7.16 (2H, m).

Reference Example 192

Preparation of 4-[4-(4-trifluoromethoxyphenoxy)-
piperidin-1-yl]phenol

A mixture of 1-[4-(tetrahydropyran-2-
15 yloxy)phenyl]-4-(4-trifluoromethoxyphenoxy)piperidine
(30.1 g, 68.8 mmol) prepared in Reference Example 191
and pyridinium p-toluene sulfonate (5.2 g, 20.6 mmol)
in ethanol (450 ml) was stirred at 70°C for 24 hours.
The reaction mixture was concentrated under reduced
20 pressure, and methylene chloride and a saturated sodium
hydrogencarbonate aqueous solution were added to the
residue, which was stirred for a while. The mixture
was extracted with methylene chloride, and the extract
was dried over magnesium sulfate, and then filtered.
25 The filtrate was concentrated under reduced pressure,
and the residue was purified by silica gel column
chromatography (methylene chloride/ethyl acetate =
10/1) to afford 4-[4-(4-trifluoromethoxyphenoxy)-

piperidin-1-yl]phenol (22.9 g, yield 94%) as a pale brown powder.

¹H-NMR (CDCl₃) δppm:

1.88 - 2.02 (2H, m), 2.06 - 2.16 (2H, m), 2.92 - 3.02
5 (2H, m), 3.30 - 3.39 (2H, m), 4.36 - 4.44 (1H, m), 4.74
(1H, s), 6.71 - 6.78 (2H, m), 6.85 - 6.94 (4H, m), 7.10
- 7.16 (2H, m).

Reference Example 193

Preparation of tert-butyl 4-[2-chloro-4-(tetrahydro-
10 pyran-2-yloxy)phenyl]piperazine-1-carboxylate

A mixture of tert-butyl piperazine-1-carboxylate (3.94 g, 21.6 mmol), 2-(4-bromo-3-chlorophenoxy)tetrahydropyran (5.61 g, 19.2 mol),
palladium acetate (86.4 mg, 0.39 mmol), BINAP (172 mg,
15 0.58 mmol) and sodium tert-butoxide (2.4 g, 25.0 mmol)
in toluene (40 ml) was refluxed under a nitrogen
atmosphere for 2 hours. Ethyl acetate and water were
added to the reaction mixture, which was stirred for a
while. The insoluble substances were removed by
20 filtration through Celite, and the filtrate was
extracted with ethyl acetate. The extract was washed
with brine, dried over magnesium sulfate, and then
filtered. The filtrate was concentrated under reduced
pressure, and the residue was purified by silica gel
25 column chromatography (n-hexane/ethyl acetate = 20/1)
to afford tert-butyl 4-[2-chloro-4-(tetrahydropyran-2-yloxy)phenyl]piperazine-1-carboxylate (4.72 g, yield
62%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 1.51 - 2.04 (6H, m), 2.88 - 2.93 (4H, m),
3.56 - 3.63. (5H, m), 3.83 - 3.94 (1H, m), 5.31 - 5.34
(1H, m), 6.88 - 6.96 (2H, m), 7.10 - 7.13 (1H, m).

5 Reference Example 194

Preparation of tert-butyl 4-(2-chloro-4-hydroxyphenyl)-
piperazine-1-carboxylate.

A mixture of tert-butyl 4-[2-chloro-4-
(tetrahydropyran-2-yloxy)phenyl]piperazine-1-
10 carboxylate (4.73 g, 11.9 mmol) prepared in Reference
Example 193 and a catalytic amount of pyridinium p-
toluene sulfonate in ethanol (50 ml) was stirred at 70°C
for 1 hour. The reaction mixture was concentrated
under reduced pressure, and methylene chloride and
15 saturated sodium hydrogencarbonate aqueous solution
were added to the residue, which was stirred for a
while. The resulting precipitates were collected by
filtration, and dried *in vacuo* to afford tert-butyl 4-
(2-chloro-4-hydroxyphenyl)piperazine-1-carboxylate
20 (2.68 g, yield 72%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.49 (9H, s), 2.87 - 2.91 (4H, m), 3.55 - 3.60 (4H, m),
5.19 (1H, br), 6.68 - 6.74 (1H, m), 6.88 - 6.93 (2H,
m).

25 Reference Example 195

Preparation of tert-butyl 4-(4-acetoxybenzoyl)-
piperazine-1-carboxylate

p-Acetoxybenzoic acid (11 g, 61.1 mmol) was

dissolved in methylene chloride (100 ml), to which DMF (3 drops) and thionyl chloride (5.54 ml, 76.3 mmol) were added, and the mixture was heated under reflux for 2 hours. The mixture was cooled in an ice-bath, to which a solution of tert-butyl piperazine-1-carboxylate (10.3 g, 55.5 mmol) and pyridine (12 ml, 0.15 mol) in methylene chloride (100 ml) was added dropwise, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with methylene chloride, and the mixture was washed with water, 10% hydrochloric acid, saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ ethyl acetate = 20/1) to afford tert-butyl 4-(4-acetoxybenzoyl)piperazine-1-carboxylate (18.5 g, yield 87%) as a colorless crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

1.47 (9H, s), 2.31 (3H, s), 3.46 (8H, br), 7.12 - 7.18 (2H, m), 7.41 - 7.46 (2H, m).

Reference Example 196

Preparation of tert-butyl 4-(4-hydroxybenzoyl)-piperazine-1-carboxylate

A mixture of tert-butyl 4-(4-acetoxybenzoyl)piperazine-1-carboxylate (18.5 g, 53.1 mmol) prepared in Reference Example 195 and potassium carbonate (370 mg, 2.65 mmol) in methanol (200 ml) was

stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, 5% hydrochloric acid and methylene chloride were added to the residue, and the mixture was vigorously stirred.

- 5 The resulting precipitates were collected by filtration, and washed with water and methylene chloride, and then dried *in vacuo* to afford tert-butyl 4-(4-hydroxybenzoyl)piperazine-1-carboxylate (14.9 g, yield 92%) as a white powder.
- 10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
1.48 (9H, s), 3.46 (4H, br), 3.60 (4H, br), 6.75 - 6.79 (2H, m), 7.22 - 7.28 (2H, m).

Reference Example 197

- Preparation of 1-benzyl-4-[4-(tetrahydropyran-2-
15 yloxy)phenyl]piperidin-4-ol

- A solution of 2-(4-bromophenoxy)-tetrahydropyran (7.2 g, 28 mmol) in THF (70 ml) was cooled to -60°C , to which n-butyl lithium (1.53 M) hexane solution (20 ml, 30.8 mmol) was added dropwise,
20 and the mixture was stirred for 30 minutes. Then, a solution of 1-benzyl-4-piperidone (5.3 g, 28 mmol) in THF (20 ml) was added dropwise to this mixture, which was stirred for 3 hours while being allowed to reach a temperature of 0°C . Saturated ammonium chloride aqueous
25 solution was added to the reaction mixture, which was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-benzyl-4-[4-(tetrahydropyran-2-yloxy)phenyl]piperidin-4-ol (5.27 g, yield 51%) as an
5 orange-colored oil.

¹H-NMR (CDCl₃) δppm:

1.52 - 2.21 (11H, m), 2.41 - 2.52 (2H, m), 2.74 - 2.78
(2H, m), 3.57 (2H, s), 3.56 - 3.63 (1H, m), 3.83 - 3.96
(1H, m), 5.39 - 5.42 (1H, m), 6.98 - 7.04 (2H, m), 7.20
10 - 7.44 (7H, m).

Reference Example 198

Preparation of tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate

A solution of 1-benzyl-4-[4-(tetrahydropyran-
15 2-yloxy)phenyl]piperidin-4-ol (1.67 g, 4.55 mmol)
prepared in Reference Example 197 in acetonitrile (45
ml) was cooled to -10°C, to which triethylsilane (2.9
ml, 18.2 mmol) and boron trifluoride diethyl ether
complex (1.1 ml, 9.1 mmol) were added, and the mixture
20 was stirred at room temperature for 2 days. Water was
added to the reaction mixture, and the mixture was
extracted with methylene chloride. The extract was
dried over magnesium sulfate, and then filtered, and
the filtrate was concentrated under reduced pressure.
25 The residue was dissolved in ethanol (50 ml), to which
a catalytic amount of 20% palladium hydroxide/carbon
was added. The mixture was stirred at room temperature
under an atmospheric pressure of hydrogen overnight.

The reaction mixture was filtered through Celite, di-tert-butyl dicarbonate (1.1 ml, 4.78 mmol) was added to the filtrate, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (1.07 g, yield 85%) as a colorless crystalline powder.

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.41 - 1.63 (2H, m), 1.49 (9H, s), 1.73 - 1.80 (2H, m), 2.50 - 2.62 (1H, m), 2.73 - 2.83 (2H, m), 4.19 - 4.24 (2H, m), 5.87 (1H, bs), 6.76 - 6.81 (2H, m), 7.02 - 7.08 (2H, m).

15 Reference Example 199

Preparation of tert-butyl 4-[3-(tetrahydropyran-2-yloxy)phenyl]piperazine-1-carboxylate

A mixture of tert-butyl piperazine-1-carboxylate (2.94 g, 15.8 mmol), 2-(3-bromophenoxy)tetrahydropyran (3.69 g, 14.4 mmol), palladium acetate (64 mg, 0.29 mmol), BINAP (285 mg, 0.43 mmol) and sodium tert-butoxide (1.8 g, 18.7 mmol) in toluene (40 ml) was refluxed under a nitrogen atmosphere for 2 hours. Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was then extracted with ethyl acetate. The extract was washed

with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1)

5 to afford tert-butyl 4-[3-(tetrahydropyran-2-yloxy)phenyl]piperazine-1-carboxylate (5.3 g, yield 99%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 1.52 - 2.04 (6H, m), 3.10 - 3.15 (4H, m),
10 3.53 - 3.64 (5H, m), 3.87 - 3.94 (1H, m), 5.38 - 5.41 (1H, m), 6.53 - 6.63 (3H, m), 7.12 - 7.19 (1H, m).

Reference Example 200

Preparation of tert-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate

15 A mixture of tert-butyl 4-[3-(tetrahydropyran-2-yloxy)phenyl]piperazine-1-carboxylate (5.20 g, 14.4 mmol) prepared in Reference Example 199 and a catalytic amount of pyridinium p-toluene sulfonate in ethanol (100 ml) was stirred at
20 70°C for 1.5 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride and a saturated sodium hydrogencarbonate aqueous solution were added to the residue, which was stirred for a while. The resulting precipitates were
25 collected by filtration, and then dried *in vacuo* to afford tert-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate (3.73 g, yield 93%) as a pale brown powder.

¹H-NMR (CDCl₃) δppm:

1.49 (9H, s), 3.09 - 3.14 (4H, m), 3.54 - 3.59 (4H, m),
5.38 (1H, br), 6.33 - 6.41 (2H, m), 6.47 - 6.52 (1H,
m), 7.08 - 7.15 (1H, m).

5 Reference Example 201

Preparation of 3-methyl-2-methylene butylaldehyde

3-methyl-2-methylene butylaldehyde was
prepared according to the method described in Journal
of American Chemical Society, 1957, p. 3267 (J. Am.
10 Chem. Soc., 3267, 1957), that is, a mixture of
isovaleraldehyde (100 ml, 932 mmol), 37% formalin (83.8
ml, 1120 mmol) and dimethylamine hydrochloride (91.2 g,
1120 mmol) was stirred at 70°C for 30 hours. The
mixture was steam distilled to separate the fraction,
15 and thus obtained aqueous layer was extracted with
diethyl ether. The extracts were combined, dried over
sodium sulfate, and filtered. The filtrate was
concentrated under reduced pressure. The residue was
distilled to afford 3-methyl-2-methylene butylaldehyde
20 (65.5 g, yield 72%) as a colorless oil.

boiling point : 105 - 115°C

¹H-NMR (CDCl₃) δppm:

1.08 (6H, d, J = 6.9 Hz), 2.75 - 2.89 (1H, m), 5.95
(1H, s), 6.24 (1H, s), 9.53 (1H, s).

25 Reference Example 202

Preparation of 3-methyl-2-methylene-butan-1-ol

A solution of 3-methyl-2-methylene
butylaldehyde (65 g, 668 mmol) prepared in Reference

Example 201 in THF (30 ml) was added dropwise to a suspension of lithium aluminum hydride (14.15 g, 373 mmol) in THF (1000 ml) while cooling in an ice-bath, and the mixture was allowed to return to room temperature, and stirred for 2 hours. While cooling, water, 15% sodium hydroxide aqueous solution, and then water were added to the reaction mixture, which was filtered. The filtrate was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 3-methyl-2-methylenebutan-1-ol (61.5 g, yield 93%) as a colorless oil.

^1H -NMR (CDCl_3) δ ppm:

1.07 (6H, d, $J = 6.9$ Hz), 1.42 (1H, t, $J = 6.1$ Hz), 2.25 - 2.43 (1H, m), 4.13 (2H, d, $J = 6.1$ Hz), 4.84 - 4.93 (1H, m), 4.98 - 5.05 (1H, m).

Reference Example 203

Preparation of 2-methoxymethoxymethyl-3-methyl-1-butene

Chloromethyl methyl ether (98 ml, 1292 mmol) and N-ethyldiisopropylamine (234 ml, 1344 mmol) were added to a solution of 3-methyl-2-methylenebutane-1-ol (61.5 g, 615 mmol) prepared in Reference Example 202 in THF (500 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 22 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in diethyl ether, and the mixture was washed with water and brine, dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced

pressure to afford 2-methoxymethoxymethyl-3-methyl-1-butene (89 g, quantitative) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.07 (6H, d, $J = 6.9$ Hz), 2.25 - 2.41 (1H, m), 3.39
5 (3H, s), 4.05 (2H, s), 4.65 (2H, s), 4.87 - 4.95 (1H, m), 5.00 - 5.05 (1H, m).

Reference Example 204

Preparation of 2-methylenebutylaldehyde

A mixture of butylaldehyde (100 ml, 1110
10 mmol), 37% formalin (99.8 ml, 1330 mmol) and dimethylamine hydrochloride (108.6 g, 1330 mmol) was stirred at 70°C for 23 hours. The mixture was steam distilled to separate the fraction, and thus obtained aqueous layer was extracted with diethyl ether. The extracts were
15 combined, dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was distilled to afford 2-methylenebutylaldehyde (66.9 g, yield 72%) as a colorless oil.

20 boiling point : 70 - 93°C

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.08 (3H, t, $J = 7.5$ Hz), 2.27 (2H, q, $J = 7.5$ Hz),
5.98 (1H, s), 6.25 (1H, s), 9.56 (1H, s).

Reference Example 205

25 Preparation of 2-methylene-1-butanol

2-Methylenebutylaldehyde (66.9 g, 796 mmol) prepared in Reference Example 204 was added dropwise to a suspension of lithium aluminum hydride (15.1 g, 398

mmol) in THF (1000 ml) while cooling in an ice-bath, and the mixture was stirred for 1 hour. Water, 15% sodium hydroxide aqueous solution and then water were added to the reaction mixture, which was filtered, and
5 the filtrate was dried over sodium sulfate. After filtration, and the filtrate was concentrated under reduced pressure to afford 2-methylene-1-butanol (65.1 g, yield 95%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

10 1.07 (3H, t, $J = 7.5$ Hz), 1.44 (1H, t, $J = 6.0$ Hz),
2.13 (2H, q, $J = 7.5$ Hz), 4.09 (2H, d, $J = 6.0$ Hz),
4.82 - 4.93 (1H, m), 4.98 - 5.07 (1H, m).

Reference Example 206

Preparation of 2-methoxymethoxymethyl-1-butene

15 Chloromethyl methyl ether (103.4 ml, 1363 mmol) and N-ethyldiisopropylamine (247.2 ml, 1419 mmol) were added to a solution of 2-methylene-1-butanol (65.1 g, 757 mmol) prepared in Reference Example 205 in THF (750 ml) while cooling in an ice-bath, and the mixture
20 was stirred at room temperature for 3 days. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in diethyl ether, and the mixture was washed with water and brine, dried over sodium sulfate, and
25 filtered. The filtrate was concentrated under reduced pressure to afford 2-methoxymethoxymethyl-1-butene (98 g, quantitative) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.07 (3H, t, $J = 7.5$ Hz), 2.09 (2H, q, $J = 7.5$ Hz),
3.38 (3H, s), 4.01 (2H, s), 4.64 (2H, s), 4.86 - 4.95
(1H, m), 5.00 - 5.05 (1H, m).

Reference Example 207

5 Preparation of tert-butyl 4-[2-oxo-2-(4-oxopiperidin-1-yl)ethyl]piperazine-1-carboxylate

1-(2-Chloroacetyl)piperidin-4-one (5.17 g,
29.4 mmol) was dissolved in acetonitrile (50 ml). To
this solution, tert-butyl piperazine-1-carboxylate
10 (5.48 g, 29.4 mmol) and N-ethyldiisopropylamine (6.2
ml, 35.3 mmol) were added, and the mixture was heated
under reflux for 2 hours. The reaction mixture was
allowed to return to room temperature, to which water
was added, and the mixture was extracted with ethyl
15 acetate. The extract was washed with brine, dried over
magnesium sulfate, and then filtered. The filtrate was
concentrated under reduced pressure, and the residue
was purified by silica gel column chromatography
(methylene chloride/methanol = 100/1) to afford tert-
20 butyl 4-[2-oxo-2-(4-oxopiperidin-1-yl)ethyl]piperazine-
1-carboxylate (6.49 g, yield 68%) as a pale yellow
crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 (9H, s), 2.44 - 2.54 (8H, m), 3.28 (2H, s), 3.42 -
25 3.47 (4H, m), 3.85 - 3.90 (4H, m).

Reference Example 208

Preparation of 4-methyl-4-pentenyl acetate

Potassium tert-butoxide (9.4 g, 84 mmol) was

added to a mixture of methyltriphenylphosphonium bromide (30 g, 84 mmol) in THF (300 ml), and the mixture was stirred at room temperature for 40 minutes. To the mixture a solution of 4-oxopentyl acetate (9.9 g, 68.8 mmol) in THF (30 ml) was gradually added dropwise while cooling in an ice-bath, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water, and extracted with diethyl ether twice. The extracts were combined, washed with brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford 4-methyl-4-pentenyl acetate (5.9 g, yield 60.4%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.70 - 1.86 (5H, m), 2.00 - 2.14 (5H, m), 4.07 (2H, t, J = 6.7 Hz), 4.69 (1H, s), 4.74 (1H, s).

20 Reference Example 209

Preparation of benzyl 4-(2-methyl-2-oxiranylmethyl)-piperazine-1-carboxylate

Trimethylsulfoxonium iodide (1.96 g, 8.91 mmol) was added to a suspension of sodium hydride (0.37 g, 9.32 mmol) in DMSO (20 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 30 minutes. To the mixture a solution of benzyl 4-(2-oxopropyl)piperazine-1-carboxylate (2.24 g, 8.10

mmol) in DMSO (10 ml) was added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into ice water, and extracted with diethyl ether. The extract was washed with water,
5 dried over magnesium sulfate, and then concentrated under reduced pressure to afford benzyl 4-(2-methyl-2-oxiranylmethyl)piperazine-1-carboxylate (1.51 g, yield 64%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

10 1.37 (3H, s), 2.27 - 2.63 (8H, m), 3.44 - 3.63 (4H, m),
5.13 (2H, s), 7.29 - 7.44 (5H, m).

Reference Example 210

Preparation of tert-butyl 4-(2-methyl-2-oxiranylmethyl)homopiperazine-1-carboxylate

15 Trimethylsulfoxonium iodide (22.95 g, 104 mmol) was gradually added to a suspension of sodium hydride (4.3 g, 109 mmol) in DMSO (200 ml), and the mixture was stirred at room temperature for 2 hours. To which a solution tert-butyl 4-(2-
20 oxopropyl)homopiperazine-1-carboxylate (24.3 g, 94.8 mmol) prepared in Reference Example 10 in DMSO (25 ml) was gradually added dropwise, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into ice water, and extracted with
25 diethyl ether. The extract was washed with water, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(2-methyl-2-oxiranyl-methyl)homopiperazine-1-carboxylate (15.38 g, yield 60%) as a pale yellow oil.

5 ^1H -NMR (CDCl_3) δ ppm:

1.38 (3H, s), 1.43 (9H, s), 1.69 - 1.90 (2H, m), 2.40 - 2.75 (8H, m), 3.36 - 3.55 (4H, m).

Reference Example 211

Preparation of tert-butyl 4-[2-(2-methyl-2-oxiranyl)-
10 ethyl]piperazine-1-carboxylate

Trimethylsulfoxonium iodide (7.8 g, 35 mmol) was gradually added to a suspension of sodium hydride (1.2 g, 35 mmol) in DMSO (120 ml), under a nitrogen atmosphere, and the mixture was stirred at room
15 temperature for 2 hours. To which a solution of tert-butyl 4-(3-oxobutyl)piperazine-1-carboxylate (6.1 g, 23.8 mmol) in DMSO (10 ml) was gradually added dropwise, and the mixture was stirred at room
20 temperature for 1.5 hours, and then at 50 to 60°C for 1.5 hours. The reaction solution was allowed to return to room temperature, poured into iced water, and extracted with ethyl acetate three times. The extracts were combined, washed with water three times and then washed with a saturated saline solution, and dried over
25 sodium sulfate. After filtration, the filtrate was concentrated under a reduced pressure to afford tert-butyl 4-[2-(2-methyl-2-oxiranyl)ethyl]piperazine-1-carboxylate (5.6 g, 87%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

1.33 (3H, s), 1.46 (9H, s), 1.66 - 1.85 (2H, m), 2.28 - 2.50 (6H, m), 2.55 - 2.66 (2H, m), 3.34 - 3.47 (4H, m).

Reference Example 212

5 Preparation of 1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethylphenyl)piperazine

Trimethylsulfoxonium iodide (2.5 g, 11.6 mmol) was gradually added to a suspension of sodium hydride (484 mg, 12.1 mmol) in dimethylsulfoxide (30 ml), and the mixture was stirred at room temperature for 1 hour. To which a solution of 1-{4-(4-trifluoromethylphenyl)piperazin-1-yl}propan-2-one (3.4 g, 11.9 mmol) in dimethylsulfoxide (20 ml) was added, and the mixture was stirred at room temperature for 1
15 hour. The reaction mixture was poured into iced water, and extracted with diethyl ether. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and then filtered. The resultant filtrate was concentrated under a reduced pressure, and
20 the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford 1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethylphenyl)piperazine (3.2 g, yield 98%) as a light yellow powder.

25 ¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 2.33 (1H, d, J = 13.0 Hz), 2.53 - 2.73 (7H, m), 3.26 - 3.30 (4H, m), 6.91 (2H, d, J = 8.7 Hz), 7.47 (2H, d, J = 8.7 Hz).

Compounds of Reference Examples 213 to 217 were prepared in the same manner as described in Reference Example 212.

Reference Example 213

- 5 1-(2-methyl-2-oxiranylmethyl)-4-(4-biphenylyl)piperazine
a pale yellow powder, yield 99%
¹H-NMR (CDCl₃) δppm:
1.41 (3H, s), 2.37 (1H, d, J = 12.9 Hz), 2.58 - 2.76
10 (7H, m), 3.23 - 3.28 (4H, m), 6.97 - 7.01 (2H, m), 7.24
- 7.30 (1H, m), 7.37 - 7.43 (2H, m), 7.49 - 7.58 (4H,
m).

Reference Example 214

- 15 1-(2-methyl-2-oxiranylmethyl)-4-(4-chlorophenyl)-
piperazine
a pale yellow powder, yield 99%
¹H-NMR (CDCl₃) δppm:
1.39 (3H, s), 2.34 (1H, d, J = 12.9 Hz), 2.54 - 2.73
(7H, m), 3.14 - 3.18 (4H, m), 6.81 - 6.87 (2H, m), 7.16
20 - 7.22 (2H, m).

Reference Example 215

- 1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethoxy-
phenyl)piperazine
a pale yellow powder, yield 99%
25 ¹H-NMR (CDCl₃) δppm:
1.40 (3H, s), 2.34 (1H, d, J = 12.9 Hz), 2.54 - 2.73
(7H, m), 3.16 - 3.20 (4H, m), 6.85 - 6.92 (2H, m), 7.08
- 7.13 (2H, m).

Reference Example 216

1-(2-methyl-2-oxiranylmethyl)-4-(pyridine-2-yl)-
piperazine

a pale yellow powder, yield 99%

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.41 (3H, s), 2.35 (1H, d, $J = 12.9$ Hz), 2.50 - 2.69
(7H, m), 3.48 - 3.60 (4H, m), 6.59 - 6.66 (2H, m), 7.43
- 7.50 (1H, m), 8.17 - 8.20 (1H, m).

Reference Example 217

10 1-(2-methyl-2-oxiranylmethyl)-4-(pyrimidin-2-yl)-
piperazine

a pale yellow powder, yield 99%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.41 (3H, s), 2.36 (1H, d, $J = 12.9$ Hz), 2.45 - 2.64
15 (7H, m), 3.81 - 3.85 (4H, m), 6.47 (1H, t, $J = 4.8$ Hz),
8.30 (2H, d, $J = 4.8$ Hz).

Reference Example 218

Preparation of tert-butyl N-methyl-[1-(2-methyl-2-
oxiranylmethyl)piperidin-4-yl]carbamate

20 Trimethylsulfoxonium iodide (1.96 g, 8.89
mmol) was gradually added to a suspension of sodium
hydride (372 mg, 9.32 mmol) in dimethylsulfoxide (20
ml), and the mixture was stirred at room temperature
for 1.5 hours. To which a solution of tert-butyl N-
25 methyl-[1-(2-oxopropyl)piperidin-4-yl]carbamate (2.3 g,
8.5 mmol) in dimethylsulfoxide (20 ml) was added, and
the mixture was stirred at room temperature for 2
hours. The reaction mixture was poured into iced

water, and extracted with diethyl ether. The extract was washed with a saturated saline solution, dried over magnesium sulfate, and then filtered. The resultant filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl N-methyl-[1-(2-methyl-2-oxiranylmethyl)piperidin-4-yl]carbamate (2.1 g, yield 86%) as a light yellow oily material.

¹H-NMR (CDCl₃) δppm:

1.36 (3H, s), 1.46 (9H, s), 1.55 - 1.79 (5H, m), 1.97 - 2.13 (2H, m), 2.30 (1H, d, J = 12.9 Hz), 2.49 (1H, d, J = 12.9 Hz), 2.59 (2H, s), 2.74 (3H, s), 2.88 - 3.06 (2H, m).

Reference Example 219

Preparation of 3-(2-methyl-2-oxiranyl)-pyridine

Using 3-acetylpyridine (8 g, 66.1 mmol), a light brown oil of 3-(2-methyl-2-oxiranyl)pyridine (7 g, yield 78.4%) was produced in the same manner as in

Reference Example 218.

¹H-NMR (CDCl₃) δppm:

1.74 (3H, s), 2.82 (1H, d, J = 5.2 Hz), 3.02 (1H, d, J = 5.2 Hz), 7.21 - 7.33 (1H, m), 7.58 - 7.70 (1H, m), 8.54 (1H, dd, 1.6 Hz, 4.8 Hz), 8.65 (1H, d, J = 2.3

Hz).

Reference Example 220

Preparation of tert-butyl 1-oxa-6-azaspiro[2,5]octane-6-carboxylate

Trimethylsulfoxonium iodide (70 g, 0.32 mol) was gradually added to a suspension of sodium hydride (13.3 g, 0.33 mol) in dimethylsulfoxide (600 ml), and the mixture was stirred at room temperature for 1 hour.

5 To which tert-butyl 4-oxo-piperidine-1-carboxylate (58 g, 0.291 mol) was gradually added, and the mixture was stirred at 55°C for 1 hour. The reaction mixture was poured into iced water, and extracted with diethyl ether. The organic phase was washed with a saturated

10 saline solution, dried over magnesium sulfate, and then filtered. The resultant filtrate was concentrated under a reduced pressure, and the residue was crystallized from n-hexane to afford tert-butyl 1-oxa-6-azaspiro[2,5]octane-6-carboxylate (61.7 g, yield 96%)

15 as a white powder.

¹H-NMR (CDCl₃) δppm:

1.40 - 1.53 (2H, m), 1.47 (9H, s), 1.72 - 1.85 (2H, m), 2.69 (2H, s), 3.37 - 3.48 (2H, m), 3.67 - 3.77 (2H, m).

Reference Example 221

20 Preparation of tert-butyl 4-[2-(1-oxa-6-azaspiro[2,5]-octan-6-yl)-2-oxoethyl]piperazine-1-carboxylate

Trimethylsulfoxonium iodide (2.02 g, 9.20 mmol) was gradually added to a suspension of sodium hydride (385 mg, 9.64 mmol) in dimethylsulfoxide (50

25 ml), and the resultant mixture was stirred at room temperature for 1 hour. To which tert-butyl 4-[2-oxo-2-(4-oxopiperidin-1-yl)ethyl]piperazine-1-carboxylate (2.85 g, 8.76 mmol) in DMSO (10 ml) was added, and the

mixture was stirred at room temperature for 2 hours, and stirred at 55°C for 1 hour. The reaction mixture was poured into iced water, and extracted with diethyl ether. The organic phase was washed with a saturated
5 saline solution, dried over magnesium sulfate, and filtered. The resultant filtrate was concentrated under a reduced pressure to afford tert-butyl 4-[2-(1-oxa-6-azaspiro[2,5]octan-6-yl)-2-oxoethyl]piperazine-1-carboxylate (2.97 g, yield 99%) as a white solid.

10 ¹H-NMR (CDCl₃) δppm:

1.45 - 1.54 (1H, m), 1.48 (9H, s), 1.78 - 1.93 (1H, m), 2.44 - 2.49 (4H, m), 2.62 (2H, s), 2.73 (2H, s), 3.42 - 3.47 (2H, m), 3.52 - 3.68 (1H, m), 3.77 - 3.88 (1H, m).

Reference Example 222

15 Preparation of 6-(4-trifluoromethylphenyl)-1-oxa-6-azaspiro[2,5]octane

Trimethylsulfoxonium iodide (2.00 g, 9.02 mmol) was gradually added to a suspension of sodium hydride (361 mg, 9.02 mmol) in dimethylsulfoxide (30
20 ml), and the mixture was stirred at room temperature for 1 hour. To which a solution of 1-(4-trifluoromethylphenyl)piperidin-4-one (2.00 g, 8.2 mmol) in DMSO (10 ml) was added, and the mixture was stirred overnight. The reaction mixture was poured
25 into ice water, and extracted with diethyl ether. The extract was washed with brine, dried over sodium sulfate, and then filtered. The residue was purified by silica gel column chromatography (n-hexane/ethyl

acetate = 5/1) to afford 6-(4-trifluoromethylphenyl)-1-oxa-6-azaspiro[2,5]octane (1.51 g, yield 72%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

- 5 1.54 - 1.65 (2H, m), 1.91 - 2.04 (2H, m), 2.54 - 2.59 (2H, m), 2.73 (2H, s), 3.38 - 3.48 (1H, m), 3.52 - 3.62 (1H, m), 6.95 (2H, d, J = 8.7 Hz), 7.48 (2H, d, J = 8.7 Hz).

Reference Example 223

- 10 Preparation of 3-(2-methyl-2-oxyranyl)propyl acetate
m-Chloroperbenzoic acid (12.3 g, 71.30 mmol) was gradually added to a solution of 4-methyl-4-pentenyl acetate (5.9 g, 41.5 mmol) prepared in Reference Example 208 in methylene chloride (60 ml)
- 15 while cooling in an ice-bath, and the mixture was stirred at room temperature for 2 hours. Saturated sodium sulfite aqueous solution and saturated sodium carbonate aqueous solution were added to the mixture while cooling in an ice-bath, which was stirred for 30
- 20 minutes, and the organic layer was separated. The aqueous layer was extracted with methylene chloride. The extracts were combined, washed with saturated sodium bicarbonate aqueous solution and brine, and dried over sodium sulfate. After filtration, the
- 25 filtrate was concentrated under reduced pressure to afford 3-(2-methyl-2-oxyranyl)propyl acetate (6.9 g, quantitative) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.33 (3H, s), 1.56 - 1.79 (4H, m), 2.05 (3H, s), 2.56 - 2.70 (2H, m), 4.08 (2H, t, J = 6.5 Hz).

Reference Example 224

Preparation of 1-ethyl-5-[2-(2-methyl-2-

5 oxiranyl)ethyl]-1H-tetrazole

m-Chloroperbenzoic acid (1.97 g, 7.99 mmol) was gradually added to a solution of 1-ethyl-5-(3-methyl-3-butenyl)-1H-tetrazole (0.95 g, 5.71 mmol) in methylene chloride (20 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 21 hours. To the reaction mixture, sodium thiosulfate aqueous solution and sodium hydrogencarbonate aqueous solution were added, and the resulting mixture was filtered. The organic layer was separated, washed with sodium hydrogencarbonate aqueous solution, dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 1-ethyl-5-[2-(2-methyl-2-oxiranyl)ethyl]-1H-tetrazole (1.2 g, quantitative) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 1.55 (3H, t, J = 7.3 Hz), 2.00 - 2.16 (1H, m), 2.20 - 2.37 (1H, m), 2.66 (2H, s), 2.78 - 2.98 (2H, m), 4.32 (2H, q, J = 7.3 Hz).

25 Using corresponding starting materials, compounds of Reference Examples 225 and 226 were prepared in the same manner as described in Reference Example 224.

Reference Example 225

1-phenyl-5-[2-(2-methyl-2-oxiranyl)ethyl]-1H-tetrazole
yield 100%

¹H-NMR (CDCl₃) δppm:

5 1.32 (3H, s), 2.01 - 2.28 (2H, m), 2.59 (2H, s), 2.92 -
2.99 (2H, m), 7.43 - 7.47 (2H, m), 7.58 - 7.63 (3H, m).

Reference Example 226

1-(4-chlorophenyl)-5-[2-(2-methyl-2-oxiranyl)ethyl]-1H-
tetrazole

10 yield 100%

¹H-NMR (CDCl₃) δppm:

1.33 (3H, s), 2.00 - 2.12 (1H, m), 2.19 - 2.31 (1H, m),
2.60 (2H, s), 2.90 - 2.97 (2H, m), 7.39 - 7.45 (2H, m),
7.56 - 7.62 (2H, m).

15 Reference Example 227

Preparation of 1-(2-methyl-2-oxiranylmethyl)-1, 4-
dihydrobenzo[d][1,3]oxazin-2-one

m-Chloroperbenzoic acid (13.76 g, 55.81 mmol)
was added to a solution of 1-(2-methyl-2-propenyl)-1,4-
20 dihydrobenzo[d][1,3]oxazin-2-one (7.09 g, 34.88 mmol)
in methylene chloride (150 ml), and the mixture was
stirred at room temperature for 24 hours. To the
mixture, sodium thiosulfate aqueous solution and sodium
hydrogencarbonate aqueous solution were added, and the
25 resulting mixture was filtered. The organic layer was
separated, washed with sodium hydrogencarbonate aqueous
solution, dried over magnesium sulfate. After
filtration, the filtrate was concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford 1-(2-methyl-2-oxiranylmethyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one (5.13 g, 67%) as a
5 pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.39 (3H, s), 2.70 (1H, d, J = 4.4 Hz), 2.78 (1H, d, J = 4.4 Hz), 3.79 (1H, d, J = 15.5 Hz), 4.51 (1H, d, J = 15.5 Hz), 5.23 (2H, s), 7.04 - 7.13 (2H, m), 7.21 -
10 7.27 (1H, m), 7.29 - 7.38 (1H, m).

Reference Example 228

Preparation of 3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

m-Chloroperbenzoic acid (1.66 g, 9.65 mmol)
15 was added to a mixture of 3-(2-methyl-2-propenyl)-3H-benzoxazol-2-one (1.66 g, 8.77 mmol) in methylene chloride (30 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the filtrate was
20 washed with a 20% sodium sulfite aqueous solution, saturated sodium bicarbonate aqueous solution and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was treated with methylene
25 chloride/n-hexane, and the resulting precipitates were collected by filtration to afford 3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one (1.78 g, yield 99%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.38 (3H, s), 2.73 (1H, d, J = 4.3 Hz), 2.81 (1H, d, J = 4.3 Hz), 3.68 (1H, d, J = 15.0 Hz), 4.26 (1H, d, J = 15.0 Hz), 7.09 - 7.29 (4H, m).

- 5 Using corresponding starting materials, compounds of Reference Examples 229 to 232 were prepared in the same manner as described in Reference Example 228.

Reference Example 229

- 10 5-chloro-3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

yield 93%

¹H-NMR (CDCl₃) δppm:

- 1.38 (3H, s), 2.75 (1H, d, J = 4.2 Hz), 2.79 (1H, d, J = 4.2 Hz), 3.60 (1H, d, J = 15.1 Hz), 4.28 (1H, d, J = 15.1 Hz), 7.05 - 7.16 (2H, m), 7.20 - 7.27 (1H, m).

Reference Example 230

5-fluoro-3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

- 20 yield 97%

¹H-NMR (CDCl₃) δppm:

- 1.38 (3H, s), 2.75 (1H, d, J = 4.3 Hz), 2.80 (1H, d, J = 4.3 Hz), 3.60 (1H, d, J = 15.1 Hz), 4.29 (1H, d, J = 15.1 Hz), 6.75 - 6.85 (1H, m), 7.01 (1H, dd, J = 2.6 Hz, 7.9 Hz), 7.13 (1H, dd, J = 4.2 Hz, 8.8 Hz).

Reference Example 231

5-phenyl-3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

yield 92%

¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 2.74 (1H, d, J = 4.3 Hz), 2.82 (1H, d, J = 4.3 Hz), 3.70 (1H, d, J = 15.0 Hz), 4.32 (1H, d, J = 15.0 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.29 - 7.49 (5H, m), 7.57 (2H, dd, J = 1.6 Hz, 8.5 Hz).

Reference Example 232

5-bromo-3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

10 yield 80%

¹H-NMR (CDCl₃) δppm:

1.38 (3H, s), 2.75 (1H, d, J = 4.2 Hz), 2.79 (1H, d, J = 4.2 Hz), 3.61 (1H, d, J = 15.1 Hz), 4.27 (1H, d, J = 15.1 Hz), 7.08 (1H, d, J = 8.5 Hz), 7.18 - 7.31 (1H, m), 7.38 (1H, d, J = 1.9 Hz).

Reference Example 233

Preparation of 1-(2-methyl-2-oxiranylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one

Using 1-(2-methyl-2-propenyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one (720 mg, 2.72 mmol), 1-(2-methyl-2-oxiranylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one (758 mg, yield 99%) as a pale yellow oil was prepared in the same manner as described in Reference Example 228.

25 ¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 2.73 (1H, d, J = 4.5 Hz), 2.86 (1H, d, J = 4.5 Hz), 3.82 (1H, d, J = 15.0 Hz), 4.38 (1H, d, J = 15.0 Hz), 7.02 - 7.30 (4H, m), 7.34 - 7.45 (1H, m),

7.50 - 7.57 (4H, m).

Using corresponding starting materials, compounds of Reference Examples 234 to 245 were prepared in the same manner as described in Reference
5 Example 233.

Reference Example 234

1-(4-fluorophenyl)-3-(2-methyl-2-oxiranylmethyl)-1, 3-dihydrobenzimidazol-2-one

yield 96%

10 ¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 2.73 (1H, d, J = 4.5 Hz), 2.85 (1H, d, J = 4.5 Hz), 3.81 (1H, d, J = 15.0 Hz), 4.38 (1H, d, J = 15.0 Hz), 7.00 - 7.30 (6H, m), 7.43 - 7.57 (2H, m).

Reference Example 235

15 1-(1-tert-butoxycarbonylpiperidin-4-yl)-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 40%

¹H-NMR (CDCl₃) δppm:

1.34 (3H, s), 1.54 (9H, s), 1.71 - 1.87 (2H, m), 2.20 -
20 2.42 (2H, m), 2.70 (1H, d, J = 4.5 Hz), 2.71 - 2.89 (3H, m), 3.75 (1H, d, J = 15.0 Hz), 4.20 - 4.53 (4H, m), 7.00 - 7.13 (3H, m), 7.15 - 7.25 (1H, m).

Reference Example 236

1-methyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one
25

yield 68%

¹H-NMR (CDCl₃) δppm:

1.34 (3H, s), 2.69 (1H, d, J = 4.5 Hz), 2.78 (1H, d, J

= 4.5 Hz), 3.44 (3H, s), 3.76 (1H, d, J = 15.0 Hz), 4.31 (1H, d, J = 15.0 Hz), 6.91 - 7.00 (1H, m), 7.05 - 5.25 (3H, m).

Reference Example 237

- 5 5-chloro-1-methyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 89%

¹H-NMR (CDCl₃) δppm:

1.34 (3H, s), 2.70 (1H, d, J = 4.4 Hz), 2.76 (1H, d, J
10 = 4.4 Hz), 3.42 (3H, s), 3.69 (1H, d, J = 15.1 Hz),
4.28 (1H, d, J = 15.1 Hz), 6.88 (1H, d, J = 8.3 Hz),
7.09 (1H, dd, J = 1.9 Hz, 8.3 Hz), 7.22 (1H, d, J = 1.9
Hz).

Reference Example 238

- 15 1-methyl-3-(2-methyl-2-oxiranylmethyl)-5-trifluoromethyl-1,3-dihydrobenzimidazol-2-one

yield 99%

¹H-NMR (CDCl₃) δppm:

1.36 (3H, s), 2.71 (1H, d, J = 4.4 Hz), 2.77 (1H, d, J
20 = 4.4 Hz), 3.47 (3H, s), 3.74 (1H, d, J = 15.1 Hz),
4.38 (1H, d, J = 15.1 Hz), 7.04 (1H, d, J = 8.2 Hz),
7.39 (1H, dd, J = 1.9 Hz, 8.2 Hz), 7.45 (1H, d, J = 1.9
Hz).

Reference Example 239

- 25 6-chloro-1-methyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazole-2-one

yield 99%

¹H-NMR (CDCl₃) δppm:

1.32 (3H, s), 2.69 (1H, d, $J = 4.6$ Hz), 2.75 (1H, d, $J = 4.6$ Hz), 3.41 (3H, s), 3.68 (1H, d, $J = 15.1$ Hz), 4.33 (1H, d, $J = 15.1$ Hz), 6.97 (1H, d, $J = 1.9$ Hz), 7.07 (1H, dd, $J = 1.9$ Hz, 8.4 Hz), 7.13 (1H, d, $J = 8.4$ Hz).

Reference Example 240

5-fluoro-1-methyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 66%

10 ^1H -NMR (CDCl_3) δ ppm:

1.34 (3H, s), 2.70 (1H, d, $J = 4.4$ Hz), 2.77 (1H, d, $J = 4.4$ Hz), 3.42 (3H, s), 3.77 (1H, d, $J = 15.0$ Hz), 4.33 (1H, d, $J = 15.0$ Hz), 6.74 - 6.91 (2H, m), 7.00 (1H, dd, $J = 2.2$ Hz, 8.6 Hz).

15 Reference Example 241

5-chloro-1-ethyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 100%

^1H -NMR (CDCl_3) δ ppm:

20 1.25 - 1.39 (6H, m), 2.70 (1H, d, $J = 4.4$ Hz), 2.76 (1H, d, $J = 4.4$ Hz), 3.69 (1H, d, $J = 15.1$ Hz), 3.93 (2H, q, $J = 7.3$ Hz), 4.30 (1H, d, $J = 15.1$ Hz), 6.90 (1H, d, $J = 8.3$ Hz), 7.07 (1H, dd, $J = 2.0$ Hz, 8.3 Hz), 7.23 (1H, d, $J = 2.0$ Hz).

25 Reference Example 242

5-chloro-1-isopropyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazole-2-one

yield 100%

¹H-NMR (CDCl₃) δppm:

1.34 (3H, s), 1.53 (6H, dd, J = 2.1 Hz, 6.7 Hz), 2.70
(1H, d, J = 4.5 Hz), 2.75 (1H, d, J = 4.5 Hz), 3.68
(1H, d, J = 15.1 Hz), 4.28 (1H, d, J = 15.1 Hz), 4.65 -
5 4.79 (1H, m), 7.04 (2H, s), 7.22 (1H, s).

Reference Example 243

5-dimethylamino-1-methyl-3-(2-methyl-2-oxiranylmethyl)-
1,3-dihydrobenzimidazol-2-one
yield 100%

10 ¹H-NMR (DMSO-d₆) δppm:

1.33 (3H, s), 2.69 (1H, d, J = 4.5 Hz), 2.79 (1H, d, J
= 4.5 Hz), 2.92 (6H, s), 3.39 (3H, s), 3.67 (1H, d, J =
15.0 Hz), 4.32 (1H, d, J = 15.0 Hz), 6.55 (1H, dd, J =
2.4 Hz, 8.6 Hz), 6.71 (1H, d, J = 2.4 Hz), 6.85 (1H, d,
15 J = 8.6 Hz).

Reference Example 244

5-chloro-1-(n-hexyl)-3-(2-methyl-2-oxiranylmethyl)-1,
3-dihydrobenzimidazol-2-one
yield 100%

20 ¹H-NMR (CDCl₃) δppm:

0.87 (3H, t, J = 6.9 Hz), 1.18 - 1.43 (9H, m), 1.64 -
1.80 (2H, m), 2.70 (1H, d, J = 4.4 Hz), 2.75 (1H, d, J
= 4.4 Hz), 3.69 (1H, d, J = 15.0 Hz), 3.86 (2H, t, J =
7.4 Hz), 4.30 (1H, d, J = 15.0 Hz), 6.88 (1H, d, J =
25 8.4 Hz), 7.06 (1H, dd, J = 1.9 Hz, 8.4 Hz), 7.22 (1H,
d, J = 1.9 Hz).

Reference Example 245

5-ethoxycarbonyl-1-methyl-3-(2-methyl-2-

oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 100%

¹H-NMR (CDCl₃) δppm:

1.32 - 1.43 (6H, m), 2.69 (1H, d, J = 4.5 Hz), 2.78
 5 (1H, d, J = 4.5 Hz), 3.47 (3H, s), 3.87 (1H, d, J =
 15.0 Hz), 4.28 (1H, d, J = 15.0 Hz), 4.39 (2H, q, J =
 7.2 Hz), 7.00 (1H, d, J = 8.2 Hz), 7.85 (1H, d, J = 1.5
 Hz), 7.90 (1H, dd, J = 1.5 Hz, 8.2 Hz).

Reference Example 246

10 Preparation of 1-benzyl-3-(2-methyl-2-oxiranylmethyl)-
 imidazolidin-2-one

Using 1-benzyl-3-(2-methyl-2-propenyl)-
 imidazolidin-2-one (1.63 g, 7.05 mmol), 1-benzyl-3-(2-
 methyl-2-oxiranylmethyl)imidazolidin-2-one (680 mg,
 15 yield 39%) as a pale yellow oil was prepared in the
 same manner as described in Reference Example 228.

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.7 Hz), 2.69 (1H, d, J
 = 4.7 Hz), 3.05 - 3.25 (3H, m), 3.27 - 3.49 (2H, m),
 20 3.61 (1H, d, J = 14.6 Hz), 4.39 (2H, s), 7.20 - 7.34
 (5H, m).

Using corresponding starting materials,
 compounds of Reference Examples 247 to 250 were
 prepared in the same manner as described in Reference
 25 Example 246.

Reference Example 247

1-(2-methyl-2-oxiranylmethyl)-3-phenylimidazolidin-2-
 one

yield 58%

¹H-NMR (CDCl₃) δppm:

1.37 (3H, s), 2.65 (1H, d, J = 4.6 Hz), 2.72 (1H, d, J = 4.6 Hz), 3.18 (1H, d, J = 14.7 Hz), 3.48 - 3.61 (2H, m), 3.64 (1H, d, J = 14.7 Hz), 3.77 - 3.91 (2H, m), 7.03 (1H, t, J = 7.3 Hz), 7.25 - 7.36 (2H, m), 7.56 (2H, d, J = 7.9 Hz).

Reference Example 248

1-(4-fluorobenzyl)-3-(2-methyl-2-oxiranylmethyl)-
imidazolidin-2-one

yield 34%

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.7 Hz), 2.68 (1H, d, J = 4.7 Hz), 3.12 (1H, d, J = 14.6 Hz), 3.16 - 3.20 (2H, m), 3.27 - 3.45 (2H, m), 3.61 (1H, d, J = 14.6 Hz), 4.35 (2H, s), 6.89 - 7.07 (2H, m), 7.14 - 7.27 (2H, m).

Reference Example 249

1-(4-bromobenzyl)-3-(2-methyl-2-oxiranylmethyl)-
imidazolidin-2-one
yield 51%

¹H-NMR (CDCl₃) δppm:

1.34 (3H, s), 2.62 (1H, d, J = 4.7 Hz), 2.67 (1H, d, J = 4.7 Hz), 3.12 (1H, d, J = 14.7 Hz), 3.16 - 3.25 (2H, m), 3.27 - 3.50 (2H, m), 3.61 (1H, d, J = 14.7 Hz), 4.33 (2H, s), 7.15 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz).

Reference Example 250

1-(4-methoxybenzyl)-3-(2-methyl-2-oxiranylmethyl)-

imidazolidin-2-one

yield 43%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.34 (3H, s), 2.61 (1H, d, $J = 4.7$ Hz), 2.67 (1H, d, $J = 4.7$ Hz), 3.07 - 3.23 (3H, m), 3.27 - 3.50 (2H, m), 3.58 (1H, d, $J = 14.6$ Hz), 3.80 (3H, s), 4.32 (2H, s), 6.86 (2H, d, $J = 8.4$ Hz), 7.19 (2H, d, $J = 8.4$ Hz).

Reference Example 251

1-(4-chlorobenzyl)-3-(2-methyl-2-oxiranylmethyl)-
10 imidazolidin-2-one

Sodium hydride (99 mg, 2.49 mmol) was added to a solution of 2-methyl-2-oxiranylmethyl toluene-4-sulfonate (500 mg, 2.37 mmol) in DMF (5 ml) while cooling in an ice-bath, and the mixture was stirred at
15 room temperature for 1 hour. To which a solution of 1-(4-chlorobenzyl)imidazolidin-2-one (633 mg, 2.61 mmol) in DMF (5 ml) was added while cooling in an ice-bath, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture,
20 and the mixture was extracted with diethyl ether twice. The extracts were combined, washed with water twice and then with brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
25 column chromatography (n-hexane/acetone = 3/1) to afford 1-(4-chlorobenzyl)-3-(2-methyl-2-oxiranylmethyl)imidazolidin-2-one (399 mg, 60%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.7 Hz), 2.68 (1H, d, J = 4.7 Hz), 3.05 - 3.25 (3H, m), 3.27 - 3.49 (2H, m), 3.61 (1H, d, J = 14.7 Hz), 4.35 (2H, s), 7.21 (2H, dd, J = 2.0 Hz, 6.7 Hz), 7.30 (2H, dd, J = 2.0 Hz, 6.7 Hz).

Using corresponding starting materials, compounds of Reference Examples 252 and 253 were prepared in the same manner as described in Reference Example 251.

10 Reference Example 252

1-(1-benzylpiperidin-4-yl)-3-(2-methyl-2-oxiranylmethyl)imidazolin-2-one

yield 54%

¹H-NMR (CDCl₃) δppm:

15 1.35 (3H, s), 1.59 - 1.80 (4H, m), 2.00 - 2.16 (2H, m), 2.60 (1H, d, J = 4.7 Hz), 2.66 (1H, d, J = 4.7 Hz), 2.84 - 3.00 (2H, m), 3.07 (1H, d, J = 14.7 Hz), 3.22 - 3.43 (4H, m), 3.50 (2H, s), 3.54 (1H, d, J = 14.7 Hz), 3.68 - 3.86 (1H, m), 7.16 - 7.34 (5H, m).

20 Reference Example 253

1-(2,4-dimethoxybenzyl)-3-(2-methyl-2-oxiranylmethyl)imidazolin-2-one

yield 40%

¹H-NMR (CDCl₃) δppm:

25 1.34 (3H, s), 2.60 (1H, d, J = 4.7 Hz), 2.67 (1H, d, J = 4.7 Hz), 3.10 (1H, d, J = 14.6 Hz), 3.14 - 3.34 (4H, m), 3.56 (1H, d, J = 14.6 Hz), 3.80 (6H, s), 4.35 (2H, s), 6.32 - 6.43 (2H, m), 7.18 (1H, d, J = 8.9 Hz).

Reference Example 254

Preparation of 1-(2-methyl-2-oxiranylmethyl)pyrrolidine-2,5-dione

Using 1-(2-methyl-2-propenyl)pyrrolidine-2,5-dione, 1-(2-methyl-2-oxiranylmethyl)pyrrolidine-2,5-dione was prepared in the same manner as described in Reference Example 228.

yield 86%

¹H-NMR (DMSO-d₆) δppm:

10 1.34 (3H, s), 2.58 (1H, d, J = 4.6 Hz), 2.67 - 2.79 (5H, m), 3.56 (1H, d, J = 13.9 Hz), 3.84 (1H, d, J = 13.9 Hz).

Reference Example 255

Preparation of 2-(2-methyl-2-oxiranylmethyl)phthalimide

15 Using 2-(2-methyl-2-propenyl)phthalimide, 2-(2-methyl-2-oxiranylmethyl)phthalimide was prepared in the same manner as described in Reference Example 228.
yield 98%

¹H-NMR (DMSO-d₆) δppm:

20 1.38 (3H, s), 2.62 (1H, d, J = 4.6 Hz), 2.82 (1H, d, J = 4.6 Hz), 3.71 (1H, d, J = 14.3 Hz), 4.01 (1H, d, J = 14.3 Hz), 7.73 (2H, dd, J = 2.9 Hz, 8.6 Hz), 7.87 (2H, dd, J = 2.9 Hz, 8.6 Hz).

Reference Example 256

25 Preparation of 1-(2-methyl-2-oxiranylmethyl)-1H-benzimidazole

Using 1-(2-methyl-2-propenyl)-1H-benzimidazole, 1-(2-methyl-2-oxiranylmethyl)-1H-

benzimidazole was prepared in the same manner as described in Reference Example 228.

yield 11%

¹H-NMR (CDCl₃) δppm:

5 1.32 (3H, s), 2.60 (1H, d, J = 4.4 Hz), 2.71 (1H, d, J = 4.4 Hz), 4.17 (1H, d, J = 15.1 Hz), 4.44 (1H, d, J = 15.1 Hz), 7.23 - 7.41 (2H, m), 7.48 (1H, dd, J = 2.2 Hz, 7.8 Hz), 7.80 (1H, dd, J = 2.2 Hz, 7.8 Hz), 7.93 (1H, s).

10 Reference Example 257

Preparation of 1-(2-methyl-2-oxiranylmethyl)-1H-imidazole

Using 1-(2-methyl-2-propenyl)-1H-imidazole, 1-(2-methyl-2-oxiranylmethyl)-1H-imidazole was prepared
15 in the same manner as described in Reference Example 228.

yield 53%

¹H-NMR (CDCl₃) δppm:

1.26 (3H, s), 2.57 (1H, d, J = 4.4 Hz), 2.69 (1H, d, J = 4.4 Hz), 3.94 (1H, d, J = 14.7 Hz), 4.16 (1H, d, J = 14.7 Hz), 6.97 (1H, s), 7.08 (1H, s), 7.49 (1H, s).

Reference Example 258

Preparation of 3-[3-(2-methyl-2-oxiranyl)propyl]-3H-benzoxazol-2-one

25 Using 3-(4-methyl-4-pentenyl)-3H-benzoxazol-2-one (3.4 g, 15.65 mmol), 3-[3-(2-methyl-2-oxiranyl)propyl]-3H-benzoxazol-2-one (3.8 g, quantitative) as a colorless crystalline powder was

prepared in the same manner as described in Reference Example 228.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.33 (3H, s), 1.56 - 1.77 (2H, m), 1.80 - 1.95 (2H, m),
5 2.59 (1H, d, $J = 4.8$ Hz), 2.63 (1H, d, $J = 4.8$ Hz),
3.85 (2H, t, $J = 7.4$ Hz), 6.99 (1H, d, $J = 7.9$ Hz),
7.05 - 7.23 (3H, m).

Reference Example 259

Preparation of 3-[4-(2-methyl-2-oxiranyl)butyl]-3H-
10 benzoxazol-2-one

Using 3-(5-methyl-5-hexenyl)-3H-benzoxazol-2-one (1.1 g, 4.8 mmol), 3-[4-(2-methyl-2-oxiranyl)butyl]-3H-benzoxazol-2-one (1.2 g, quantitative) as a colorless oil was prepared in the
15 same manner as described in Reference Example 228.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.30 (3H, s), 1.42 - 1.67 (4H, m), 1.74 - 1.88 (2H, m),
2.57 (1H, d, $J = 4.9$ Hz), 2.60 (1H, d, $J = 4.9$ Hz),
3.84 (2H, t, $J = 7.2$ Hz), 6.98 (1H, d, $J = 8.1$ Hz),
20 7.02 - 7.30 (3H, m).

Reference Example 260

Preparation of 3-(2-methyl-2-oxiranylmethyl)oxazolidin-
2-one

25 Using 3-(2-methyl-2-propenyl)oxazolidin-2-one (4.28 g, 30.35 mmol), 3-(2-methyl-2-oxiranylmethyl)-oxazolidin-2-one (2.87 g, yield 62%) as a colorless oil was prepared by the method in Reference Example 228.

¹H-NMR (CDCl₃) δppm:

1.36 (3H, s), 2.66 (1H, d, J = 4.5 Hz), 2.70 (1H, d, J = 4.5 Hz), 3.15 (1H, d, J = 14.7 Hz), 3.57 - 3.75 (3H, m), 4.25 - 4.39 (2H, m).

5 Reference Example 261

Preparation of 3,3-difluoro-1-(2-methyl-2-oxiranylmethyl)-1,3-dihydroindol-2-one

Using 3,3-difluoro-1-(2-methyl-2-propenyl)-1,3-dihydroindol-2-one (1.08 g, 4.83 mmol), 3,3-difluoro-1-(2-methyl-2-oxiranylmethyl)-1,3-dihydroindol-2-one (1.14 g, yield 99%) as a pale yellow powder was prepared in the same manner as described in Reference Example 228.

¹H-NMR (CDCl₃) δppm:

15 1.35 (3H, s), 2.71 (1H, d, J = 4.3 Hz), 2.77 (1H, d, J = 4.3 Hz), 3.46 (1H, d, J = 15.0 Hz), 4.26 (1H, d, J = 15.0 Hz), 7.12 - 7.24 (2H, m), 7.45 - 7.61 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 262 and 263 were prepared in the same manner as described in Reference Example 261.

Reference Example 262

3,3-dimethyl-1-(2-methyl-2-oxiranylmethyl)-1,3-dihydroindol-2-one

25 ¹H-NMR (CDCl₃) δppm:

1.31 (3H, s), 1.39 (6H, s), 2.67 (1H, d, J = 4.5 Hz), 2.74 (1H, d, J = 4.5 Hz), 3.53 (1H, d, J = 14.0 Hz), 4.22 (1H, d, J = 14.0 Hz), 7.00 - 7.10 (2H, m), 7.16 -

7.31 (2H, m).

Reference Example 263

1-(2-methyl-2-oxiranylmethyl)-1,3-dihydroindol-2-one

¹H-NMR (CDCl₃) δppm:

5 1.34 (3H, s), 2.67 (1H, d, J = 4.5 Hz), 2.76 (1H, d, J = 4.5 Hz), 3.49 - 3.61 (3H, m), 4.22 (1H, d, J = 14.9 Hz), 7.00 - 7.10 (2H, m), 7.18 - 7.35 (2H, m).

Reference Example 264

Preparation of benzyl (2-methyl-2-oxiranylmethyl)-

10 carbamate

Benzyl N-(2-methyl-2-propenyl)carbamate (3.90 g, 19.0 mmol) prepared in Reference Example 173 was dissolved in methylene chloride (80 ml), to which m-chloroperbenzoic acid (5.15 g, 20.9 mmol) was added, 15 and the mixture was stirred at room temperature overnight. Sodium thiosulfate aqueous solution and saturated sodium hydrogencarbonate aqueous solution were added to the reaction mixture, which was stirred for a while. The organic layer was separated, washed 20 with saturated sodium hydrogencarbonate aqueous solution, dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford benzyl(2-methyl-2-oxiranylmethyl)carbamate (4.31 g, quantitative) as a colorless oil.

25 ¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.61 (1H, d, J = 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 3.28 - 3.53 (2H, m), 4.90 (1H, br), 5.11 (2H, s), 7.26 - 7.44 (5H, m).

Using corresponding starting materials, compounds of Reference Examples 265 to 276 were prepared in the same manner as described in Reference Example 264.

5 Reference Example 265

benzyl N-methyl-N-(2-methyl-2-oxiranylmethyl)carbamate
yield 42%

¹H-NMR (CDCl₃) δppm:

1.26 (1.5H, s), 1.31 (1.5H, s), 2.57 (1H, s), 2.61 (1H,
10 s), 2.99 (3H, s), 3.24 (1H, d, J = 15.1 Hz), 3.62
(0.5H, d, J = 15.1 Hz), 3.72 (0.5H, d, J = 15.1 Hz),
5.14 (2H, s), 7.27 - 7.41 (5H, m).

Reference Example 266

4-chlorobenzyl(2-methyl-2-oxiranylmethyl)carbamate
15 yield 98%

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.4 Hz), 2.71 (1H, d, J
= 4.4 Hz), 3.27 - 3.50 (2H, m), 4.88 (1H, br), 5.06
(2H, s), 7.23 - 7.41 (4H, m).

20

Reference Example 267

4-fluorobenzyl(2-methyl-2-oxiranylmethyl)carbamate
yield 100%

¹H-NMR (CDCl₃) δppm:

25 1.34 (3H, s), 2.61 (1H, d, J = 4.5 Hz), 2.71 (1H, d, J
= 4.5 Hz), 3.32 - 3.50 (2H, m), 4.86 (1H, br), 5.06
(2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m).

Reference Example 268

ethyl(2-methyl-2-oxiranylmethyl)carbamate

yield 82%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, t, J = 7.1 Hz), 1.35 (3H, s), 2.62 (1H, d, J
5 = 4.5 Hz), 2.74 (1H, d, J = 4.5 Hz), 3.27 - 3.50 (2H,
m), 4.12 (2H, q, J = 7.1 Hz), 4.78 (1H, br).

Reference Example 269

4-trifluoromethoxybenzyl(2-methyl-2-oxiranylmethyl)-
carbamate

10 yield 99%

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.4 Hz), 2.71 (1H, d, J
= 4.4 Hz), 3.42 (2H, d, J = 5.6 Hz), 4.90 (1H, br),
5.10 (2H, s), 7.20 (2H, d, J = 8.3 Hz), 7.38 (2H, d, J
15 = 8.3 Hz).

Reference Example 270

4-fluorobenzyl N-methyl-N-(2-methyl-2-oxiranylmethyl)-
carbamate

yield 73%

20 ¹H-NMR (CDCl₃) δppm:

1.25 (1.5H, s), 1.30 (1.5H, s), 2.56 (1H, s), 2.61 (1H,
s), 2.97 (3H, s), 3.22 (1H, d, J = 14.8 Hz), 3.61
(0.5H, d, J = 14.8 Hz), 3.72 (0.5H, d, J = 14.8 Hz),
5.10 (2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m).

25

Reference Example 271

4-chlorobenzyl oxiranylmethylcarbamate

yield 97%

¹H-NMR (CDCl₃) δppm:

2.59 (1H, dd, $J = 2.6$ Hz, 4.6 Hz), 2.79 (1H, t, $J = 4.3$ Hz), 3.11 (1H, br), 3.20 - 3.32 (1H, m), 3.50 - 3.73 (1H, m), 4.93 (1H, br), 5.07 (2H, s), 7.23 - 7.41 (4H, m).

5 Reference Example 272

4-fluorobenzyl oxiranylmethylcarbamate

yield 89%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.59 (1H, dd, $J = 2.6$ Hz, 4.6 Hz), 2.79 (1H, t, $J = 4.3$ Hz), 3.11 (1H, br), 3.21 - 3.32 (1H, m), 3.45 - 3.73 (1H, m), 4.92 (1H, br), 5.07 (2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m).

Reference Example 273

4-fluorobenzyl N-methyl-N-oxiranylmethylcarbamate

15 yield 34%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.51 (1H, br), 2.76 (1H, br), 3.01 (3H, s), 3.02 - 3.27 (2H, m), 3.55 - 3.91 (1H, m), 5.10 (2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m).

20

Reference Example 274

tert-butyl oxiranylmethylcarbamate

yield 83%

$^1\text{H-NMR}$ (CDCl_3) δppm :

25 1.45 (9H, s), 2.59 (1H, dd, $J = 2.6$ Hz, 4.6 Hz), 2.78 (1H, t, $J = 4.4$ Hz), 3.09 (1H, br), 3.16 - 3.28 (1H, m), 3.38 - 3.66 (1H, br), 4.53 - 4.91 (1H, br).

Reference Example 275

benzyl oxiranylmethylcarbamate

yield 72%

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

2.67 (1H, t, $J = 4.5$ Hz), 2.91 - 3.32 (4H, m), 4.91 -
5 5.09 (3H, m), 7.23 - 7.55 (5H, m).

Reference Example 276

phenyl oxiranylmethylcarbamate

Yield 90%

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

10 2.57 (1H, dd, $J = 2.5$ Hz, 5.0 Hz), 2.73 (1H, t, $J = 4.5$
Hz), 3.00 - 3.45 (3H, m), 7.10 (2H, d, $J = 7.6$ Hz),
7.20 (1H, t, $J = 7.6$ Hz), 7.38 (2H, t, $J = 7.6$ Hz),
7.94 (1H, br).

Reference Example 277

15 Preparation of (2-methyl-2-oxiranylmethyl)(4-chloro-
phenyl)carbamate

m-Chloroperbenzoic acid (1.6 g, 6.6 mmol) was
added to a solution of 2-methyl-2-propenyl(4-
chlorophenyl)carbamate (1.0 g, 4.4 mmol) in methylene
20 chloride (20 ml) while cooling in an ice-bath, and the
mixture was stirred at room temperature for 4 hours.
To which sodium thiosulfate aqueous solution was added
and the mixture was filtered, and sodium
hydrogencarbonate aqueous solution was added to the
25 filtrate. The organic layer was separated, dried over
magnesium sulfate, and concentrated under reduced
pressure to afford (2-methyl-2-oxiranylmethyl)(4-
chlorophenyl)carbamate (1.1 g, quantitative) as a pale

yellow crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

1.42 (3H, s), 2.71 (1H, d, $J = 4.6$ Hz), 2.82 (1H, d, $J = 4.6$ Hz), 4.01 (1H, d, $J = 11.9$ Hz), 4.37 (1H, d, $J =$
5 11.9 Hz), 6.79 (1H, br), 7.23 - 7.37 (4H, m).

Reference Example 278

Preparation of (2-methyl-2-oxiranylmethyl) N-(4-chlorophenyl)-N-methylcarbamate

m-Chloroperbenzoic acid (2.5 g, 10.1 mmol)
10 was added to a solution of 2-methyl-2-propenyl N-(4-chlorophenyl)-N-methylcarbamate (1.78 g, 6.7 mmol) in methylene chloride (20 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 6.5 hours. To which sodium thiosulfate aqueous
15 solution was added and the mixture was filtered, and sodium hydrogencarbonate aqueous solution was added to the filtrate. The organic layer was separated, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was
20 purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford (2-methyl-2-oxiranylmethyl) N-(4-chlorophenyl)-N-methylcarbamate (1.7 g, quantitative) as a pale yellow oil.

^1H -NMR (CDCl_3) δ ppm:

25 1.32 (3H, s), 2.62 (1H, d, $J = 4.6$ Hz), 2.69 (1H, d, $J = 4.6$ Hz), 3.30 (3H, s), 3.99 (1H, d, $J = 11.8$ Hz), 4.30 (1H, d, $J = 11.8$ Hz), 7.15 - 7.25 (2H, m), 7.31 - 7.38 (2H, m).

Reference Example 279

Preparation of tert-butyl 4-oxiranylmethylpiperazine-1-carboxylate

A mixture of tert-butyl piperazine-1-carboxylate (6.2 g, 33.29 mmol), epibromohydrin (5.4 g, 39.42 mmol) and potassium carbonate (5.5 g, 39.79 mmol) in acetonitrile (70 ml) was heated under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue. The mixture was extracted with methylene chloride. The extract was washed with brine, dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to afford tert-butyl 4-oxiranylmethylpiperazine-1-carboxylate (6.2 g, yield 77%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 (9H, s), 2.21 - 2.60 (6H, m), 2.70 - 2.81 (2H, m), 3.05 - 3.12 (1H, m), 3.35 - 3.56 (4H, m).

Reference Example 280

Preparation of tert-butyl[4-(2-methyl-2-oxiranylmethyl)piperazin-1-yl]carbamate

A mixture of (2-methyl-2-oxiranylmethyl)toluene-4-sulfonate (9.75 g, 40.3 mmol), tert-butyl piperazin-1-yl-carbamate (6.75 g, 33.5 mmol) prepared in Reference Example 36, triethylamine (7 ml, 50.3 mmol) and potassium iodide (6.68 g, 33.5 mmol) in DMF

(70 ml) was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The extract was washed with water and brine, dried over sodium sulfate, and filtered.

- 5 The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/acetone = 4/1) to afford tert-butyl[4-(2-methyl-2-oxiranylmethyl)piperazin-1-yl]carbamate (4.66 g, yield 51%) as a colorless
10 crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 1.46 (9H, s), 2.31 (1H, d, J = 12.9 Hz),
2.49 - 2.84 (11H, m), 5.37 (1H, br).

Reference Example 281

- 15 Preparation of 3-(2-methyl-2-oxiranylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

A mixture of 5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (3.18 g, 12.92 mmol) prepared in Reference Example 49, (2-methyl-2-oxiranylmethyl)
20 toluene-4-sulfonate (4.80 g, 19.38 mmol), potassium carbonate (2.14 g, 15.50 mmol) and sodium iodide (2.90 g, 19.38 mmol) in DMF (30 ml) was stirred at room temperature for 24 hours, and then at 60°C for 4 hours. The reaction mixture was poured into water, and
25 extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromato-

graphy (hexane/ethyl acetate = 9/1) to afford 3-(2-methyl-2-oxiranylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (2.37 g, yield 58%) as a colorless crystalline powder.

5 ^1H -NMR (DMSO- d_6) δ ppm:

1.43 (3H, s), 2.72 (1H, d, J = 4.4 Hz), 2.86 (1H, d, J = 4.4 Hz), 3.93 (2H, dd, J = 14.8 Hz, 22.2 Hz), 7.28 - 7.41 (2H, m), 7.83 - 7.98 (2H, m).

Using 5-substituted-3H-[1,3,4]oxadiazol-2-one
10 and (2-methyl-2-oxiranylmethyl) toluene-4-sulfonate, compounds of Reference Examples 282 to 289 were prepared in the same manner as described in Reference Example 281.

Reference Example 282

15 3-(2-methyl-2-oxiranylmethyl)-5-phenyl-3H-[1,3,4]-oxadiazol-2-one
yield 41%

^1H -NMR (CDCl_3) δ ppm:

1.44 (3H, s), 2.72 (1H, d, J = 4.5 Hz), 2.88 (1H, d, J = 4.5 Hz), 3.87 (1H, d, J = 14.7 Hz), 3.99 (1H, d, J = 14.7 Hz), 7.40 - 7.57 (3H, m), 7.79 - 7.87 (2H, m).

Reference Example 283

3-(2-methyl-2-oxiranylmethyl)-5-(4-trifluoromethylphenyl)-3H-[1,3,4]oxadiazol-2-one

25 Yield 34%

^1H -NMR (CDCl_3) δ ppm:

1.45 (3H, s), 2.73 (1H, d, J = 4.5 Hz), 2.87 (1H, d, J = 4.5 Hz), 3.92 (1H, d, J = 14.8 Hz), 4.00 (1H, d, J =

14.8 Hz), 7.75 (2H, d, $J = 8.3$ Hz), 8.01 (2H, d, $J = 8.3$ Hz).

Reference Example 284

3-(2-methyl-2-oxiranylmethyl)-5-(4-biphenylyl)-3H-

5 [1,3,4]oxadiazol-2-one

yield 38%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.45 (3H, s), 2.73 (1H, d, $J = 4.5$ Hz), 2.89 (1H, d, $J = 4.5$ Hz), 3.89 (1H, d, $J = 14.8$ Hz), 4.00 (1H, d, $J =$
10 14.8 Hz), 7.33 - 7.50 (3H, m), 7.57 - 7.75 (4H, m),
7.93 (2H, d, $J = 8.6$ Hz).

Reference Example 285

3-(2-methyl-2-oxiranylmethyl)-5-(4-chlorophenyl)-3H-

[1,3,4]oxadiazol-2-one

15 yield 52%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.44 (3H, s), 2.72 (1H, d, $J = 4.4$ Hz), 2.86 (1H, d, $J = 4.4$ Hz), 3.89 (1H, d, $J = 14.8$ Hz), 3.97 (1H, d, $J =$
14.8 Hz), 7.46 (2H, d, $J = 8.7$ Hz), 7.80 (2H, d, $J =$
20 8.7 Hz).

Reference Example 286

3-(2-methyl-2-oxiranylmethyl)-5-(4-fluorophenyl)-3H-

[1,3,4]oxadiazol-2-one

yield 72%

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.43 (3H, s), 2.72 (1H, d, $J = 4.5$ Hz), 2.87 (1H, d, $J = 4.5$ Hz), 3.88 (1H, d, $J = 14.7$ Hz), 3.96 (1H, d, $J =$
14.7 Hz), 7.11 - 7.21 (2H, m), 7.74 - 7.89 (2H, m).

Reference Example 287

3-(2-methyl-2-oxiranylmethyl)-5-[2-(4-chlorophenyl)-ethyl]-3H-[1,3,4]oxadiazol-2-one

yield 78%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.32 (3H, s), 2.64 (1H, d, $J = 4.5$ Hz), 2.72 (1H, d, $J = 4.5$ Hz), 2.79 - 2.90 (2H, m), 2.93 - 3.04 (2H, m), 3.74 (1H, d, $J = 14.8$ Hz), 3.79 (1H, d, $J = 14.8$ Hz), 7.12 (2H, d, $J = 8.6$ Hz), 7.27 (2H, d, $J = 8.6$ Hz).

10 Reference Example 288

3-(2-methyl-2-oxiranylmethyl)-5-[2-(4-chlorophenyl)vinyl]-3H-[1,3,4]oxadiazol-2-one

yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

15 1.41 (3H, s), 2.71 (1H, d, $J = 4.4$ Hz), 2.83 (1H, d, $J = 4.4$ Hz), 3.88 (2H, s), 6.60 (1H, d, $J = 16.4$ Hz), 7.28 - 7.47 (5H, m).

Reference Example 289

3-(2-methyl-2-oxiranylmethyl)-5-(4-chlorophenoxy-methyl)-3H-[1,3,4]oxadiazol-2-one

20 yield 59%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.37 (3H, s), 2.68 (1H, d, $J = 4.4$ Hz), 2.78 (1H, d, $J = 4.4$ Hz), 3.86 (2H, s), 4.90 (2H, s), 6.91 (2H, dd, $J = 2.3$ Hz, 6.9 Hz), 7.29 (2H, dd, $J = 2.3$ Hz, 6.9 Hz).

Reference Example 290

Preparation of 2-(2-methyl-2-oxiranylmethyl)-1,1-dioxo-1,2-dihydrobenzo[d]isothiazol-3-one

Using saccharin and (2-methyl-2-oxiranylmethyl) toluene-4-sulfonate, 2-(2-methyl-2-oxiranylmethyl)-1,1-dioxo-1,2-dihydrobenzo[d]isothiazol-3-one was prepared in the
 5 same manner as described in Reference Example 281.
 a colorless crystalline powder, yield 43%

¹H-NMR (CDCl₃) δppm:

1.49 (3H, s), 2.74 (1H, d, J = 4.5 Hz), 2.96 (1H, d, J = 4.5 Hz), 3.73 (1H, d, J = 15.5 Hz), 4.04 (1H, d., J =
 10 15.5 Hz), 7.81 - 8.00 (3H, m), 8.09 (1H, dd, J = 2.4 Hz, 6.6 Hz).

Reference Example 291

Preparation of 1-(2-methyl-2-oxiranylmethyl)piperidin-4-one

15 Using 4-piperidone hydrochloride monohydrate-hydrate, 1-(2-methyl-2-oxiranylmethyl)piperidin-4-one was prepared in the same manner as described in Reference Example 281.
 a colorless oil, yield 50%

20 ¹H-NMR (CDCl₃) δppm:

1.43 (3H, s), 2.35 - 2.51 (5H, m), 2.58 - 2.93 (7H, m).

Reference Example 292

Preparation of 4-(2-methyl-2-oxiranylmethyl)-1-(4-trifluoromethylbenzyl)piperazin-2-one

25 Using 1-(4-trifluoromethylbenzyl)piperazin-2-one, 4-(2-methyl-2-oxiranylmethyl)-1-(4-trifluoromethylbenzyl)piperazin-2-one was prepared in the same manner as described in Reference Example 281.

a colorless crystalline powder, yield 63%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.37 (3H, s), 2.34 (1H, d, $J = 12.9$ Hz), 2.53 - 2.67
(4H, m), 2.77 - 2.91 (1H, m), 3.14 - 3.37 (4H, m), 4.62
5 (1H, d, $J = 15.1$ Hz), 4.69 (1H, d, $J = 15.1$ Hz), 7.38
(2H, d, $J = 8.2$ Hz), 7.60 (2H, d, $J = 8.2$ Hz).

Reference Example 293

Preparation of 4-(2-methyl-2-oxiranylmethyl)-1-(tert-butyl)piperazin-2-one

10 Using 1-(tert-butyl)piperazin-2-one, 4-(2-methyl-2-oxiranylmethyl)-1-(tert-butyl)piperazin-2-one was prepared in the same manner as described in Reference Example 281.

a colorless crystalline powder, yield 39%

15 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.38 (3H, s), 1.45 (9H, s), 2.31 (1H, d, $J = 12.9$ Hz),
2.42 - 2.55 (4H, m), 2.74 - 2.88 (1H, m), 3.02 (1H, d,
 $J = 16.1$ Hz), 3.20 (1H, d, $J = 16.1$ Hz), 3.28 - 3.37
(2H, m).

20 Reference Example 294

Preparation of (S)-1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethoxyphenyl)piperazine

A solution of (2-methyl-2-oxiranylmethyl) (R)-toluene-4-sulfonate (0.80 g, 3.30 mmol), 1-(4-
25 trifluoromethoxyphenyl)piperazine (0.91 g, 3.36 mmol), and triethylamine (0.55 ml, 3.96 mmol) in DMF (8 ml) was stirred at room temperature for 22 hours. The reaction mixture was poured into water, and extracted

with ethyl acetate, washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =
5 100/1) to afford (S)-1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethoxyphenyl)piperazine (0.46 g, yield 44%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.40 (3H, s), 2.34 (1H, d, $J = 12.9$ Hz), 2.52 - 2.77
10 (7H, m), 3.10 - 3.27 (4H, m), 6.81 - 6.94 (2H, m), 7.06 - 7.17 (2H, m).

Reference Example 295

Preparation of ethyl(S)-1-(2-methyl-2-oxiranylmethyl)-piperidine-4-carboxylate

15 A solution of (2-methyl-2-oxiranylmethyl) (R)-toluene-4-sulfonate (13.5 g, 55.8 mmol), ethyl piperidine 4-carboxylate (8.9 g, 50.9 mmol), and triethylamine (6.5 g, 64.4 mmol) in DMF (70 ml) was stirred at room temperature for 2 days. The reaction
20 mixture was poured into water, and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column
25 chromatography (n-hexane/ethyl acetate = 3/1) to afford ethyl(S)-1-(2-methyl-2-oxiranylmethyl)piperidine-4-carboxylate (5.4 g, yield 47%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.25 (3H, t, $J = 7.1$ Hz), 1.36 (3H, s), 1.67 - 1.93 (4H, m), 1.97 - 2.08 (2H, m), 2.19 - 2.37 (2H, m), 2.48 (1H, d, $J = 11.5$ Hz), 2.58 (2H, s), 2.78 - 2.97 (2H, m), 4.13 (2H, q, $J = 7.1$ Hz).

- 5 Using corresponding starting materials, compounds of Reference Examples 296 to 299 were prepared in the same manner as described in Reference Example 295.

Reference Example 296

- 10 4-trifluoromethylbenzyl(S)-1-(2-methyl-2-oxiranylmethyl)piperidine-4-carboxylate
a colorless oil, yield 18%
 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
1.35 (3H, s), 1.69 - 2.10 (6H, m), 2.25 - 2.37 (1H, m),
15 2.28 (1H, d, $J = 12.9$ Hz), 2.48 (1H, d, $J = 12.9$ Hz),
2.58 (2H, s), 2.81 - 3.00 (2H, m), 5.11 (2H, s), 7.20 (2H, d, $J = 8.0$ Hz), 7.38 (2H, d, $J = 8.0$ Hz).

Reference Example 297

- 20 4-chlorobenzyl(S)-1-(2-methyl-2-oxiranylmethyl)piperidine-4-carboxylate
a colorless oil, yield 26%
 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
1.36 (3H, s), 1.75 - 2.16 (7H, m), 2.27 (1H, d, $J =$
25 12.9 Hz), 2.50 (1H, d, $J = 12.9$ Hz), 2.58 (2H, s), 2.87 - 3.09 (2H, m), 5.13 (2H, s), 7.17 - 7.21 (2H, m), 7.27 - 7.31 (2H, m).

Reference Example 298

N-(4-chlorobenzyl) (S)-1-(2-methyl-2-oxiranylmethyl)
piperidine-4-carboxamide

a colorless oil, yield 26%

¹H-NMR (CDCl₃) δppm:

- 5 1.36 (3H, s), 1.75 - 2.16 (7H, m), 2.27 (1H, d, J =
12.9 Hz), 2.50 (1H, d, J = 12.9 Hz), 2.58 (2H, s), 2.87
- 3.09 (2H, m), 4.41 (2H, d, J = 5.8 Hz), 5.78 (1H,
br), 7.17 - 7.21 (2H, m), 7.27 - 7.31 (2H, m).

Reference Example 299

- 10 N-(4-chlorophenyl) (S)-1-(2-methyl-2-oxiranyl-
methyl)piperidine-4-carboxamide

a colorless oil, yield 33%

¹H-NMR (CDCl₃) δppm:

- 1.37 (3H, s), 1.82 - 2.08 (6H, m), 2.13 - 2.27 (1H, m),
15 2.30 (1H, d, J = 13.0 Hz), 2.53 (1H, d, J = 13.0 Hz),
2.60 (2H, s), 2.93 - 3.12 (2H, m), 7.16 (1H, bs), 7.26
- 7.31 (2H, m), 7.45 - 7.49 (2H, m).

Reference Example 300

- 20 Preparation of 5-(2-methyl-2-oxiranylmethylsulfanyl)-1-
phenyl-1H-tetrazole

A mixture of 1-phenyl-5-mercapto-1H-tetrazole
(3.5 g, 19.64 mmol), (2-methyl-2-oxiranylmethyl)
toluene-4-sulfonate (5 g, 20.64 mmol), potassium
25 carbonate (3 g, 21.71 mmol), and sodium iodide (4.5 g,
30.02 mmol) in DMF (30 ml) was stirred at 60°C for 6
hours. The reaction mixture was poured into water,
and extracted with ethyl acetate twice. The extracts

were combined, washed with 5% sodium hydroxide aqueous solution and then with water three times, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue
5 was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford 5-(2-methyl-2-oxiranylmethylsulfanyl)-1-phenyl-1H-tetrazole (1.9 g, yield 39%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

10 1.46 (3H, s), 2.73 (1H, d, J = 4.5 Hz), 2.91 (1H, d, J = 4.5 Hz), 3.61 (1H, d, J = 13.9 Hz), 3.77 (1H, d, J. = 13.9 Hz), 7.50 - 7.65 (5H, m).

Reference Example 301

Preparation of tert-butyl 3-(2-methyl-2-oxiranyl)-
15 propionate

Trimethylsulfoxonium iodide (19.54 g, 88.78 mmol) was added to a suspension of sodium hydride (3.71 g, 92.82 mmol) in DMSO (50 ml) while cooling in an ice-bath, and the mixture was stirred for 2.5 hours. To
20 which a solution of tert-butyl 4-oxopentanoate (13.90 g, 80.71 mmol) in DMSO (20 ml) was added, and the mixture was stirred at room temperature for 15 hours. The mixture was poured into ice water, extracted with diethyl ether. The extract was washed with water,
25 dried over magnesium sulfate, and concentrated under reduced pressure to afford tert-butyl 3-(2-methyl-2-oxiranyl)propionate (10.1 g, yield 67%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.32 (3H, s), 1.44 (9H, s), 1.85 - 1.94 (2H, m), 2.27 - 2.33 (2H, m), 2.58 (1H, d, J = 4.7 Hz), 2.63 (1H, d, J = 4.7 Hz).

5 Reference Example 302

Preparation of 2-isopropyl-2-methoxymethoxymethyloxirane

m-Chloroperbenzoic acid (213 g, 861 mmol) was gradually added to a solution of 2-methoxymethoxymethyl-3-methyl-1-butene (89 g, 615 mmol) in methylene chloride (800 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was washed with 10% potassium sulfide aqueous solution and sodium hydrogencarbonate aqueous solution, dried over sodium sulfate, and then concentrated under reduced pressure to afford 2-isopropyl-2-methoxymethoxymethyloxirane (98 g, quantitative) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

20 0.95 (3H, d, J = 7.0 Hz), 1.02 (3H, d, J = 7.0 Hz), 1.84 - 2.05 (1H, m), 2.66 (1H, d, J = 4.9 Hz), 2.75 (1H, d, J = 4.9 Hz), 3.37 (3H, s), 3.63 (1H, d, J = 11.3 Hz), 3.70 (1H, d, J = 11.3 Hz), 4.62 (2H, s).

Reference Example 303

25 Preparation of 2-ethyl-2-methoxymethoxymethyloxirane

m-Chloroperbenzoic acid (143.7 g, 833 mmol) was gradually added to a solution of 2-methoxymethoxymethyl-1-butene (98 g, 757 mmol) prepared

in Reference Example 206 in methylene chloride (8800 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature overnight. The reaction mixture was washed with water, 10% sodium sulfide

5 aqueous solution and sodium hydrogencarbonate aqueous solution, dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 2-ethyl-2-methoxymethoxymethyloxirane (111 g, quantitative) as a colorless oil.

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

0.96 (3H, t, $J = 7.5$ Hz), 1.60 - 1.73 (1H, m), 1.77 - 1.93 (1H, m), 2.66 (1H, d, $J = 4.8$ Hz), 2.74 (1H, d, $J = 4.8$ Hz), 3.37 (3H, s), 3.56 (1H, d, $J = 11.2$ Hz), 3.65 (1H, d, $J = 11.2$ Hz), 4.64 (2H, s).

15 Reference Example 304

Preparation of 2-(2-methoxymethoxyethyl)oxirane

m-Chloroperbenzoic acid (20.6 g, 95.6 mmol) was gradually added to a solution of 4-methoxymethoxy-1-butene (10.46 g, 90.1 mmol) in methylene chloride
20 (250 ml) while cooling in an ice-bath, the mixture was stirred at room temperature for 6 hours. The reaction mixture was filtered, and the filtrate was washed with a 10% sodium sulfide aqueous solution and sodium hydrogencarbonate aqueous solution, dried over
25 magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(2-methoxymethoxyethyl) oxirane (10.3 g, 86%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.69 - 1.96 (2H, m), 2.53 (1H, dd, J = 2.7 Hz, 4.9 Hz),
2.79 (1H, t, J = 4.9 Hz), 3.02 - 3.08 (1H, m), 3.38
(3H, s), 3.68 (2H, t, J = 5.9 Hz), 4.64 (2H, s).

5 Reference Example 305

Preparation of 4-(4-trifluoromethylphenoxy)piperidine-
1-carbonylchloride

A mixture of 4-(4-trifluoromethylphenoxy)
piperidine (0.6 g, 2.45 mmol), triphosgene (0.25 g,
10 0.86 mmol), and pyridine (0.4 ml, 4.90 mmol) in toluene
(6 ml) was heated under reflux for 2.5 hours. To which
ethyl acetate was added, and the mixture was washed
with 10% hydrochloric acid, dried over magnesium
sulfate. After filtration, the filtrate was
15 concentrated under reduced pressure to afford 4-(4-
trifluoromethylphenoxy)piperidine-1-carbonylchloride
(0.72 g, yield 96%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.79 - 2.10 (4H, m), 3.50 - 3.96 (4H, m), 4.58 - 4.75
20 (1H, m), 6.97 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8
Hz).

Reference Example 306

Preparation of 4-(4-trifluoromethylphenylamino)-
piperidine-1-carbonylchloride

25 A mixture of (4-trifluoromethylphenylamino)-
piperidine (1.14 g, 4.67 mmol), triphosgene (0.55 g,
1.87 mmol), and triethylamine (0.98 ml, 7.01 mmol) in
methylene chloride (10 ml) was stirred at room

temperature for 1.5 hours. The reaction mixture was washed with water, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 4-(4-

5 trifluoromethylphenylamino)piperidine-1-carbonylchloride (1.43 g, quantitative) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.33 - 1.65 (2H, m), 2.09 - 2.24 (2H, m), 3.02 - 3.22 (1H, m), 3.22 - 3.41 (1H, m), 3.48 - 3.70 (1H, m), 4.20
10 - 4.35 (2H, m), 6.66 (2H, d, J = 8.5 Hz), 7.43 (2H, d, J = 8.5 Hz).

As shown in Reference Example 305 or 306, amines, cyclic amines, and benzene-condensed heterocyclic compounds were allowed to react in the
15 presence of triphosgene and triethylamine or pyridine to afford compounds of Reference Examples 307 to 324.

Reference Example 307

5-chloro-2,3-dihydroindole-1-carbonylchloride

20 a pale yellow crystalline powder, yield 100%

¹H-NMR (CDCl₃) δppm:

3.19 (2H, t, J = 8.3 Hz), 4.28 (2H, t, J = 8.3 Hz),
7.18 - 7.22 (2H, m), 7.80 (1H, d, J = 9.5 Hz).

Reference Example 308

25 6-chloro-3,4-dihydro-1H-isoquinoline-2-carbonylchloride

a pale yellow oil, yield 100%

¹H-NMR (CDCl₃) δppm:

2.83 - 3.00 (2H, m), 3.83 (1H, t, J = 6.0 Hz), 3.90

(1H, t, J = 6.0 Hz), 4.71 (1H, s), 4.80 (1H, s), 7.06 (1H, d, J = 8.0 Hz), 7.13 - 7.28 (2H, m).

Reference Example 309

6-chloro-3,4-dihydro-2H-quinoline-1-carbonylchloride

5 a yellow oil, yield 100%

¹H-NMR (CDCl₃) δppm:

1.99 - 2.09 (2H, m), 2.79 (2H, t, J = 6.5 Hz), 3.94 (2H, t, J = 6.3 Hz), 7.14 - 7.20 (2H, m), 7.62 (1H, d, J = 8.5 Hz).

10 Reference Example 310

5-chloro-1,3-dihydroisoindole-2-carbonylchloride

a yellow oil, yield 100%

¹H-NMR (CDCl₃) δppm:

3.19 (2H, t, J = 8.3 Hz), 4.28 (2H, t, J = 8.3 Hz),
15 7.18 - 7.22 (2H, m), 7.80 (1H, d, J = 9.5 Hz).

Reference Example 311

tert-butyl 4-chlorocarbonylpiperazine-1-carboxylate

a pale yellow crystalline powder, yield 100%

¹H-NMR (CDCl₃) δppm:

20 1.47 (9H, s), 3.16 - 3.29 (2H, m), 3.37 - 3.55 (4H, m),
3.55 - 3.78 (2H, m).

Reference Example 312

4-(4-trifluoromethoxybenzyloxycarbonyl)piperazine-1-carbonylchloride

25 Yield 100%

¹H-NMR (CDCl₃) δppm:

3.43 - 3.80 (8H, m), 5.15 (2H, s), 7.15 - 7.25 (2H, m),
7.33 - 7.45 (2H, m).

Reference Example 313

4-[3-(4-trifluoromethylphenyl)-2-propenyloxycarbonyl]-
piperazine-1-carbonylchloride

Yield 100%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.54 - 3.65 (4H, m), 3.65 - 3.72 (2H, m), 3.72 - 3.83
(2H, m), 4.80 (2H, dd, $J = 1.1 \text{ Hz}$, 6.1 Hz), 6.39 (1H,
dt, $J = 6.1 \text{ Hz}$, 15.9 Hz), 6.68 (1H, d, $J = 15.9 \text{ Hz}$),
7.49 (2H, d, $J = 8.4 \text{ Hz}$), 7.59 (2H, d, $J = 8.4 \text{ Hz}$).

10 Reference Example 314

4-(4-chlorobenzyl)piperazine-1-carbonylchloride

a brown oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.65 - 2.96 (4H, m), 3.67 - 4.08 (6H, m), 7.36 - 7.39

15 (4H, m).

Reference Example 315

4-(4-trifluoromethylbenzyl)piperazine-1-carbonyl-
chloride

a brown oil, yield 100%

20 $^1\text{H-NMR}$ (CDCl_3) δppm :

2.97 - 3.12 (4H, m), 3.91 - 4.06 (2H, m), 4.06 - 4.21
(2H, m), 4.15 (2H, s), 7.58 - 7.73 (4H, m).

Reference Example 316

4-(4-trifluoromethoxybenzyl)piperazine-1-carbonyl-
25 chloride

a brown oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.58 - 2.85 (4H, m), 3.58 - 3.90 (6H, m), 7.17 - 7.25

(2H, m), 7.35 - 7.46 (2H, m).

Reference Example 317

4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydro-
pyridine-1-carbonylchloride

5 a pale brown oil, yield 57%

¹H-NMR (CDCl₃) δppm:

2.54 - 2.67 (2H, m), 3.85 (1H, t, J = 5.7 Hz), 3.94
(1H, t, J = 5.7 Hz), 4.28 (1H, d, J = 2.7 Hz), 4.36
(1H, d, J = 2.7 Hz), 5.94 - 6.06 (1H, m), 7.16 - 7.21

10 (2H, m), 7.36 - 7.41 (2H, m).

Reference Example 318

4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine-1-
carbonylchloride

a pale brown oil, yield 60%

15 ¹H-NMR (CDCl₃) δppm:

2.54 - 2.67 (2H, m), 3.51 (1H, t, J = 5.6 Hz), 3.81
(3H, s), 3.92 - 4.02 (1H, m), 4.23 - 4.31 (1H, m), 4.31
- 4.37 (1H, m), 5.87 - 5.96 (1H, m), 6.85 - 6.90 (2H,
m), 7.29 - 7.35 (2H, m).

20 Reference Example 319

4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-
1-carbonylchloride

a pale brown oil, yield 100%

¹H-NMR (CDCl₃) δppm:

25 2.58 - 2.71 (2H, m), 3.87 (1H, t, J = 5.7 Hz), 3.96
(1H, t, J = 5.7 Hz), 4.31 (1H, d, J = 2.8 Hz), 4.39
(1H, d, J = 2.8 Hz), 6.04 - 6.15 (1H, m), 7.45 - 7.63
(4H, m).

Reference Example 320

4-(4-bromophenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride

a pale brown oil, yield 100%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

2.52 - 2.67 (2H, m), 3.84 (1H, t, $J = 5.7$ Hz), 3.93 (1H, t, $J = 5.7$ Hz), 4.27 (1H, d, $J = 2.6$ Hz), 4.35 (1H, d, $J = 2.6$ Hz), 5.94 - 6.06 (1H, m), 7.21 - 7.24 (2H, m), 7.43 - 7.49 (2H, m).

10 Reference Example 321

4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride

a pale brown oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

15 2.54 - 2.67 (2H, m), 3.84 (1H, t, $J = 5.7$ Hz), 3.93 (1H, t, $J = 5.7$ Hz), 4.27 (1H, d, $J = 2.6$ Hz), 4.35 (1H, d, $J = 2.6$ Hz), 5.90 - 6.00 (1H, m), 7.00 - 7.07 (2H, m), 7.24 - 7.35 (2H, m).

Reference Example 322

20 N-(4-chlorophenyl)-N-cyclohexylcarbamyylchloride

a pale yellow crystalline powder, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

0.79 - 1.06 (1H, m), 1.14 (2H, t, $J = 3.5$ Hz, 12.5 Hz), 1.23 - 1.44 (2H, m), 1.50 - 65 (1H, m), 1.67 - 1.81 (2H, m), 1.87 - 2.00 (2H, m), 4.78 (1H, m), 7.06 - 7.10 (2H, m), 7.36 - 7.41 (2H, m).

Reference Example 323

N-methyl-N-(4-trifluoromethoxybenzyl)carbamyylchloride

a yellow oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.09 (3H, s), 4.58 (2H, s), 7.16 - 7.33 (4H, m).

Reference Example 324

5 4-[(4-trifluoromethylbenzylidene)amino]piperazine-1-carbonylchloride

a brown oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.17 - 3.39 (4H, m), 3.74 - 4.02 (4H, m), 7.56 (1H, s),

10 7.60 (2H, d, $J = 8.3$ Hz), 7.69 (2H, d, $J = 8.3$ Hz).

Reference Example 325

Preparation of 4-(4-trifluoromethoxyphenyl)piperazine-1-carbonylchloride

A mixture of 1-(4-trifluoromethoxyphenyl)

15 piperazine (1.0 g, 4.1 mmol), triphosgene (0.42 g, 1.4 mmol), and pyridine (0.66 ml, 8.2 mmol) in toluene (20 ml) was stirred at 100°C for 4.5 hours. To which ethyl acetate was added, and the mixture was washed with water, dried over magnesium sulfate. After filtration,
20 the filtrate was concentrated under reduced pressure to afford 4-(4-trifluoromethoxyphenyl)piperazine-1-carbonylchloride (1.3 g, quantitative) as a brown oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.08 - 3.30 (4H, m), 3.67 - 4.00 (4H, m), 6.79 - 6.98

25 (2H, m), 7.08 - 7.17 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 326 to 332 were quantitatively prepared in the same manner as described

in Reference Example 325.

Reference Example 326

4-(4-trifluoromethylphenyl)piperazine-1-carbonylchloride

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.26 - 3.39 (4H, m), 3.76 - 3.87 (2H, m), 3.87 - 3.98 (2H, m), 6.87 - 6.98 (2H, m), 7.48 - 7.59 (2H, m).

Reference Example 327

4-(4-methoxyphenyl)piperazine-1-carbonylchloride

10 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.04 - 3.15 (4H, m), 3.52 - 3.75 (2H, m), 3.75 - 3.92 (2H, m), 3.78 (3H, s), 6.81 - 6.98 (4H, m).

Reference Example 328

4-(4-chlorophenyl)piperazine-1-carbonylchloride

15 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.10 - 3.25 (4H, m), 3.37 - 3.52 (2H, m), 3.73 - 3.90 (2H, m), 6.83 - 6.88 (2H, m), 7.20 - 7.25 (2H, m).

Reference Example 329

4-(3-chlorophenyl)piperazine-1-carbonylchloride

20 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.15 - 3.29 (4H, m), 3.73 - 3.94 (4H, m), 6.77 - 6.81 (1H, m), 6.88 - 6.91 (2H, m), 7.20 (1H, t, $J = 8.3$ Hz).

Reference Example 330

4-(3,4-dichlorophenyl)piperazine-1-carbonylchloride

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.08 - 3.27 (4H, m), 3.37 - 3.48 (2H, m), 3.60 - 3.73 (1H, m), 3.73 - 3.90 (1H, m), 6.75 (1H, dd, $J = 2.9$ Hz, 9.0 Hz), 6.96 - 6.98 (1H, m), 7.30 (1H, dd, $J = 5.1$ Hz,

9.0 Hz).

Reference Example 331

4-(4-fluorophenyl)piperazine-1-carbonylchloride

¹H-NMR (CDCl₃) δppm:

- 5 3.04 - 3.19 (4H, m), 3.40 - 3.50 (2H, m), 3.62 - 3.75 (1H, m), 3.75 - 3.92 (1H, m), 6.86 - 7.03 (4H, m).

Reference Example 332

4-(3-trifluoromethylphenyl)piperazine-1-carbonylchloride

10 ¹H-NMR (CDCl₃) δppm:

- 3.21 - 3.35 (4H, m), 3.42 - 3.54 (2H, m), 3.77 - 3.96 (2H, m), 7.02 - 7.19 (3H, m), 7.31 - 7.46 (1H, m).

Reference Example 333

Preparation of tert-butyl 4-[1-(4-trifluoromethoxy-
15 phenyl)piperidin-4-yl]piperazine-1-carboxylate

- A mixture of tert-butyl 4-piperidin-4-ylpiperazine-1-carboxylate (1.5 g, 5.67 mmol), 4-(trifluoromethoxy)bromobenzene (3.36 g, 13.92 mmol), palladium acetate (25 mg, 0.11 mmol), BINAP (87 mg,
20 0.14 mmol), and sodium tert-butoxide (1.07 g, 11.14 mmol) in toluene (20 ml) was stirred at 80°C under a nitrogen atmosphere for 8 hours. The reaction mixture was allowed to return to room temperature, to which ethyl acetate (10 ml) and brine (20 ml) were added, and
25 the mixture was filtered. The organic layer was separated, and dried over sodium sulfate. After filtration, the filtrate was concentrated, and the residue was purified by silica gel column

chromatography (methylene chloride/methanol = 20/1) to afford tert-butyl 4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazine-1-carboxylate (1.01 g, 42%) as a yellow powder.

5 $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm

1.49(9H, s), 1.52-1.75(2H, m), 1.83-1.99(2H, m), 2.31-2.52(5H, m), 2.64-2.81(2H, m), 3.36-3.49(4H, m), 3.62-3.75(2H, m), 6.86(2H, d, $J = 8.5$ Hz), 7.09(2H, d, $J = 8.5$ Hz).

10 Reference Example 334

Preparation of 1-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazine

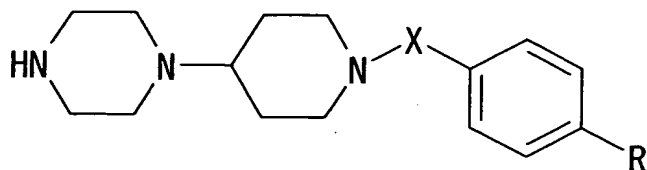
Tert-butyl 4-[1-(4-trifluoromethoxyphenyl)-piperidin-4-yl]piperazine-1-carboxylate (1 g, 2.33 mmol) was dissolved in methylene chloride (10 ml), to which trifluoroacetic acid (10 ml) was added while cooling in an ice-bath, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was washed with a 25% sodium hydroxide aqueous solution (40 ml) and brine (10 ml), and dried over sodium sulfate. After filtration, the filtrate was concentrated to afford 1-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazine (770 mg, quantitative) as a yellow amorphous form.

25 $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm

1.52-1.75(2H, m), 1.83-1.99(2H, m), 2.25-2.38(1H, m), 2.48-2.76(6H, m), 2.79-2.99(4H, m), 3.56-3.75(2H, m), 6.89(2H, d, $J = 8.5$ Hz), 7.09(2H, d, $J = 8.5$ Hz).

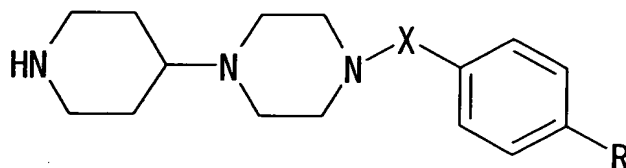
Following compounds were prepared in the same manner as described in Reference Example 334.

Table 1



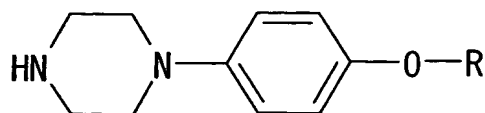
| Reference Example | X | R | ¹ H-NMR (CDCl ₃) δ ppm |
|-------------------|-----------------|------------------|---|
| 335 | none | OCF ₃ | 1.52-1.75 (2H, m), 1.83-1.99 (2H, m), 2.25-2.35 (1H, m), 2.48-2.76 (6H, m), 2.79-2.99 (4H, m), 3.56-3.75 (2H, m), 6.89 (2H, d, J=8.5Hz), 7.09 (2H, d, J=8.5Hz) |
| 336 | C=O | Cl | 1.31-1.55 (2H, m), 1.69-1.98 (2H, m), 2.36-2.60 (5H, m), 2.69-3.00 (6H, m), 3.69-3.86 (1H, m), 4.55-4.79 (1H, m), 7.24-7.43 (4H, m) |
| 337 | C=O | OCF ₃ | 1.31-1.60 (2H, m), 1.71-2.00 (2H, m), 2.38-2.60 (5H, m), 2.67-3.07 (6H, m), 3.62-3.86 (1H, m), 4.57-4.83 (1H, m), 7.25 (2H, d, J=2.3Hz, 8.7Hz), 7.45 (2H, d, J=2.3Hz, 8.7Hz). |
| 338 | CH ₂ | Cl | 1.45-1.60 (2H, m), 1.67-1.83 (2H, m), 1.86-2.00 (2H, m), 2.12-2.24 (1H, m), 2.45-2.57 (4H, m), 2.79-2.93 (6H, m), 3.44 (2H, s), 7.14-7.31 (4H, m) |
| 339 | CH ₂ | OCF ₃ | 1.48-1.81 (4H, m), 1.85-2.00 (2H, m), 2.12-2.29 (1H, m), 2.43-2.57 (4H, m), 2.76-2.98 (6H, m), 3.46 (2H, s), 7.15 (2H, d, J=8.5Hz), 7.33 (2H, d, J=8.5Hz) |

Table 2



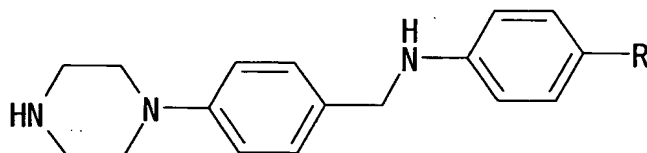
| Reference Example | X | R | ¹ H-NMR (CDCl ₃) δ ppm |
|-------------------|-----------------|------------------|--|
| 340 | C=O | Cl | 1.29-1.48 (2H, m), 1.67-1.86 (2H, m), 2.31-2.69 (7H, m), 3.07-3.21 (2H, m), 3.31-3.50 (2H, m), 3.60-3.83 (2H, m), 7.26-7.45 (4H, m) |
| 341 | C=O | OCF ₃ | 1.31-1.50 (2H, m), 1.64-1.83 (2H, m), 2.29-2.69 (7H, m), 3.07-3.21 (2H, m), 3.31-3.50 (2H, m), 3.64-3.83 (2H, m), 7.25 (2H, d, J=8.7Hz), 7.45 (2H, d, J=8.7Hz) |
| 342 | CH ₂ | OCF ₃ | 1.25-1.48 (2H, m), 1.69-1.86 (2H, m), 2.19-2.62 (11H, m), 3.00-3.17 (2H, m), 3.50 (2H, s), 7.15 (2H, d, J=8.6Hz), 7.34 (2H, d, J=8.6Hz) |
| 343 | CH ₂ | Cl | 1.24-1.43 (2H, m), 1.74-1.86 (2H, m), 2.21-2.60 (11H, m), 3.02-3.17 (2H, m), 3.46 (2H, s), 7.19-7.33 (4H, m) |
| 344 | none | OCF ₃ | 1.31-1.51 (2H, m), 1.76-1.93 (2H, m), 2.29-2.45 (1H, m), 2.52-2.79 (6H, m), 3.10-3.26 (6H, m), 6.88 (2H, d, J=8.6Hz), 7.10 (2H, d, J=8.6Hz). |
| 345 | none | Cl | 1.33-1.52 (2H, m), 1.81-1.98 (2H, m), 2.26-2.43 (1H, m), 2.52-2.74 (6H, m), 3.05-3.21 (6H, m), 6.84 (2H, d, J=6.9Hz), 7.19 (2H, d, J=6.9Hz) |

Table 3



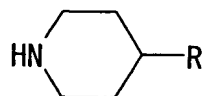
| Reference Example | R | ¹ H-NMR (CDCl ₃) δ ppm |
|-------------------|--|--|
| 346 | 4-ClPh- | 2.98-3.12 (8H, m), 6.80-6.94 (6H, m), 7.24 (2H, d, J=2.3Hz, 6.8Hz) |
| 347 | 4-CF ₃ PhCH ₂ - | 3.04 (8H, s), 5.08 (2H, s), 6.90 (4H, s), 7.54 (2H, d, J=8.2Hz), 7.63 (2H, d, J=8.2Hz) |
| 348 | 4-ClPhCH ₂ - | 3.03 (8H, s), 4.98 (2H, s), 6.89 (4H, s), 7.35 (4H, s). |
| 349 | 4-CF ₃ OPhCH ₂ - | 3.04 (8H, s), 5.01 (2H, s), 6.90 (4H, s), 7.22 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.5Hz) |
| 350 | 4-CF ₃ OPh- | 2.96-3.14 (8H, m), 6.82-6.98 (6H, m), 7.06-7.16 (2H, m) |
| 351 | 4-CF ₃ Ph- | 2.96-3.14 (8H, m), 6.84-7.00 (6H, m), 7.53 (2H, d, J=8.6Hz) |

Table 4



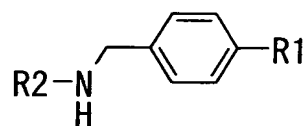
| Reference Example | R | ¹ H-NMR (CDCl ₃) δ ppm |
|-------------------|--------------------|--|
| 352 | Cl- | 2.96-3.16 (8H, m), 3.97 (1H, br), 4.20 (1H, d, J=5.4Hz), 6.55 (1H, d, J=8.8Hz), 6.60 (1H, d, J=8.8Hz), 6.90 (1H, d, J=8.8Hz), 7.00-7.14 (4H, m), 7.18-7.25 (1H, m) |
| 353 | CF ₃ O- | 2.94-3.20 (8H, m), 4.00 (1H, br), 4.21 (1H, d, J=5.3Hz), 6.57 (1H, d, J=6.8Hz), 6.64 (1H, d, J=8.8Hz), 6.80-7.12 (5H, m), 7.16-7.25 (1H, m) |

Table 5



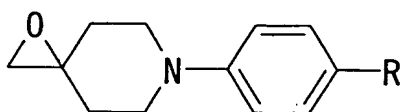
| Reference Example | R | ¹ H-NMR (CDCl ₃) δ ppm |
|----------------------|---|---|
| 354 | | 1.51-1.73 (2H, m), 1.76-1.92 (2H, m), 2.51-2.82 (3H, m), 3.10-3.27 (2H, m), 6.92-7.08 (4H, m), 7.12-7.27 (2H, m), 7.56 (2H, d, J=8.6Hz) |
| 355 | | 1.33-1.60 (4H, m), 1.69-2.02 (4H, m), 2.29-2.64 (5H, m), 2.76-2.88 (2H, m), 3.05-3.17 (2H, m), 4.14-4.31 (1H, m), 6.85 (2H, d, J=8.7Hz), 7.12 (2H, d, J=8.7Hz) |
| 356 | | 1.52-1.98 (4H, m), 2.26-2.43 (1H, m), 2.55-2.74 (2H, m), 3.10-3.26 (2H, m), 7.18 (2H, d, J=8.4Hz), 7.55 (2H, d, J=8.4Hz) |
| 357 | | 1.60-1.81 (4H, m), 2.57-2.74 (3H, m), 3.05-3.21 (6H, m), 3.60-3.83 (4H, m), 6.90 (2H, d, J=8.4Hz), 7.13 (2H, d, J=8.4Hz) |
| 358 | | 1.56-1.73 (2H, m), 1.83-1.89 (3H, m), 2.57-2.82 (3H, m), 3.18-3.24 (2H, m), 6.95-7.05 (4H, m), 7.20-7.25 (2H, m), 7.53-7.57 (2H, m) |
| 359 | | 1.57-1.86 (4H, m), 2.52-2.81 (4H, m), 3.19-3.25 (2H, m), 5.03 (2H, s), 6.89-6.94 (2H, m), 7.11-7.25 (4H, m), 7.44-7.48 (2H, m) |
| 360 | | 1.51-1.68 (3H, m), 1.78-1.84 (2H, m), 2.50-2.64 (1H, m), 2.67-2.79 (2H, m), 3.15-3.21 (2H, m), 5.11 (1H, s), 6.87-6.94 (2H, m), 7.12-7.18 (2H, m), 7.52-7.57 (2H, m), 7.62-7.66 (2H, m) |
| 361 | | 1.60-2.12 (5H, m), 2.52-2.66 (1H, m), 2.71-2.83 (2H, m), 3.22-3.28 (2H, m), 5.01 (2H, s), 6.88-6.93 (2H, m), 7.11-7.18 (2H, m), 7.30-7.41 (4H, m) |
| 362 | | 1.86-2.18 (3H, m), 2.35-2.52 (1H, m), 2.61-2.69 (1H, m), 2.93-3.01 (5H, m), 3.24-3.59 (3H, m), 4.49 (2H, s), 6.67-6.70 (2H, m), 7.07-7.17 (4H, m), 7.23-7.27 (2H, m) |

Table 6



| Reference Example | R1 | R2 | ¹ H-NMR (CDCl ₃) δ ppm |
|-------------------|----|-------------------------------|--|
| 363 | | CH ₃ | 1.50 (9H, s), 2.44 (3H, s), 3.00–3.14 (4H, m), 3.49–3.57 (4H, m), 3.72 (2H, s), 6.89 (2H, d, J=7.2 Hz), 7.26 (2H, d, J=7.2 Hz). |
| 364 | | C ₂ H ₅ | 1.15 (3H, t, J=7.1 Hz), 1.48 (9H, s), 2.18 (1H, brs), 2.69 (2H, q, J=7.1 Hz), 3.09–3.12 (4H, m), 3.55–3.59 (4H, m), 3.73 (2H, s), 6.86–6.92 (2H, m), 7.23–7.26 (2H, m). |
| 365 | | CH ₃ | 1.09–1.16 (3H, m), 1.78–1.88 (2H, m), 2.49 (3H, s), 2.73–2.80 (2H, m), 3.17–3.31 (3H, m), 3.62–3.79 (5H, m), 3.92 (2H, s), 6.67–6.70 (2H, m), 6.91–6.93 (2H, m), 7.13–7.19 (2H, m), 7.39–7.42 (2H, m). |

Table 7



| Reference Example | R | ¹ H-NMR (CDCl ₃) δ ppm |
|-------------------|-------------------|---|
| 366 | -Cl | 1.51-1.67 (2H, m), 1.90-2.04 (2H, m), 2.72 (2H, s), 3.18-3.43 (4H, m), 6.89 (2H, d, J=8.4Hz), 7.21 (2H, d, J=8.4Hz) |
| 367 | -OCF ₃ | 1.53-1.67 (2H, m), 1.86-2.04 (2H, m), 2.73 (2H, s), 3.22-3.45 (4H, m), 6.93 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.4Hz). |
| 368 | | 1.53-1.63 (2H, m), 1.90-2.06 (2H, m), 2.73 (2H, s), 3.24 (3H, s), 3.27-3.45 (4H, m), 6.72 (2H, d, J=8.4Hz), 6.90-7.10 (6H, m). |
| 369 | | 1.54-1.69 (2H, m), 1.92-2.06 (2H, m), 2.73 (2H, s), 3.20-3.43 (4H, m), 6.84-6.96 (6H, m), 7.14 (2H, d, J=8.4Hz) |
| 370 | | 1.58-1.69 (2H, m), 1.88-2.15 (6H, m), 2.71 (2H, s), 2.90-3.04 (2H, m), 3.17-3.44 (6H, m), 4.31-4.46 (1H, m), 6.85-6.94 (6H, m), 7.14 (2H, d, J=8.4Hz) |
| 371 | | 1.55-1.71 (2H, m), 1.92-2.04 (2H, m), 2.72 (2H, s), 3.12-3.35 (12H, m), 6.86-7.00 (6H, m), 7.14 (2H, d, J=8.5Hz). |

Following compounds were prepared in the same manner as described in Reference Example 186.

Reference Example 372

1-(4-Hydroxyphenyl)-4-phenylpiperidin-4-ol

5 MS: 269 (M⁺)

Reference Example 373

4-(4-chlorophenyl)-1-(4-hydroxyphenyl)piperidin-4-ol

MS: 349 ($M^+ - 1$)

Reference Example 374

5 1-(4-hydroxyphenyl)-4-(4-trifluoromethoxy-
phenyl)piperidin-4-ol

MS: 353 (M^+)

Reference Example 375

(4-hydroxyphenyl)-[4-(4-trifluoromethoxyphenoxy)-
10 piperidin-1-yl]methanone

MS: 381 (M^+)

Reference Example 376

tert-butyl 1-(4-hydroxyphenyl)piperidine-4-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ ppm 1.46 (9H, s), 1.76-2.05 (4H, m), 2.23-
15 2.34 (1H, m), 2.62-2.73 (2H, m), 3.39-3.48 (2H, m), 4.39-
4.49 (1H, m), 4.78 (1H, s), 6.72-6.78 (2H, m), 6.82-
6.89 (2H, m).

Reference Example 377

4-(4-phenylpiperidin-1-yl)phenol

20 MS: 253 (M^+)

Reference Example 378

4-(4,4-diethoxypiperidin-1-yl)phenol

MS: 265 (M^+)

Reference Example 379

25 2-dimethylaminomethyl-4-[4-(4-trifluoromethoxy-
phenoxy)piperidin-1-yl]phenol

MS: 410 (M^+)

Reference Example 380

4-(4-[1,3]dioxolan-2-ylpiperidin-1-yl)phenol

¹H NMR(CDCl₃) δppm 1.51-1.70(2H, m), 1.80-1.92(2H, m),
2.53-2.66(2H, m), 3.48-3.57(2H, m), 3.84-3.92(2H, m),
5 3.92-4.02(2H, m), 4.63(1H, brs), 4.69(1H, d, J = 4.9
Hz), 6.70-6.78(2H, m), 6.83-6.91(2H, m).

Reference Example 381

4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]phenol

MS: 337(M⁺)

10 Reference Example 382

tert-butyl 4-(4-hydroxyphenoxy)piperidine-1-carboxylate

MS: 293(M⁺)

Reference Example 383

4-[1-(4-trifluoromethylphenyl)piperidin-4-yloxy]phenol

15 MS: 337(M⁺)

Reference Example 384

4-(1,4-dioxa-8-azaspiro[4,5]decan-8-yl)phenol

¹H NMR(CDCl₃) δppm 1.87(4H, t, J = 5.7 Hz), 3.18(4H, t,
J = 5.7 Hz), 3.99(4H, s), 6.74(2H, d, J = 8.9 Hz),
20 6.88(2H, d, J = 8.9 Hz).

Reference Example 385

4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)phenol

MS: 251(M⁺)

Reference Example 386

25 tert-butyl 4-(4-hydroxyphenyl)piperazine-1-carboxylate

¹H NMR(CDCl₃) δppm 1.49(9H, s), 2.95-3.00(4H, m), 3.55-
3.60(4H, m), 5.77(1H, s), 6.74-6.86(4H, m).

Reference Example 387

4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]phenol

¹H NMR(CDCl₃) δppm 3.19-3.24(4H, m), 3.29-3.34(4H, m),
 4.51(1H, s), 6.76-6.82(2H, m), 6.87-6.97(4H, m), 7.11-
 5 7.16(2H, m).

Reference Example 388

4-{4-[(4-trifluoromethoxybenzylidene)amino]piperazin-1-yl}phenol

MS: 349(M⁺-1)

10 Reference Example 389

4-[4-(4-chlorobenzyl)piperazin-1-yl]phenol

¹H NMR(CDCl₃) δppm 2.60(4H, t, J = 4.8 Hz), 3.08(4H, t,
 J = 4.8 Hz), 3.53(2H, s), 6.71-6.78(2H, m), 6.81-
 6.89(2H, m), 7.27-7.42(4H, m).

15 Reference Example 390

3-(4-hydroxyphenyl)oxazolidin-2-one

¹H NMR(CDCl₃) δppm 3.94-4.01(2H, m), 4.35-4.42(2H, m),
 6.73-6.80(2H, m), 7.29-7.36(2H, m), 9.34(1H, s).

Reference Example 391

20 4-(4-pyridyl)phenol

¹H NMR(CDCl₃) δppm 6.87-6.93(2H, m), 7.60-7.70(4H, m),
 8.54-8.57(2H, m), 9.85(1H, s).

Reference Example 392

4-hydroxy-N-(4-trifluoromethoxyphenyl)benzamide

25 ¹H NMR(CDCl₃) δppm 6.84-6.87(2H, m), 7.31-7.34(2H, m),
 7.83-7.87(4H, m), 10.11(1H, brs), 10.15(1H, brs).

Reference Example 393

(4-hydroxyphenyl)-(4-trifluoromethoxyphenyl)methanone

^1H NMR(CDCl_3) δ ppm 6.08(1H, s), 6.92-6.96(2H, m), 7.30-7.33(2H, m), 7.76-7.83(4H, m).

Reference Example 394

(4-hydroxyphenyl)-(4-trifluoromethylphenyl)methanone

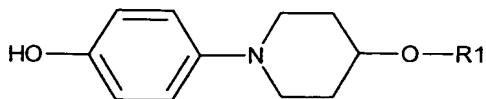
5 MS: 266(M^+)

Reference Example 395

4-(4-trifluoromethoxyphenoxy)phenol

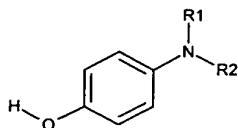
^1H NMR(CDCl_3) δ ppm 4.67(1H, brs), 6.81-6.85(2H, m), 6.90-6.96(4H, m), 7.13-7.16(2H, m).

Table 8



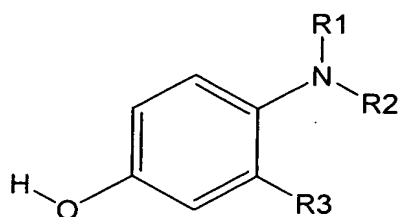
| Refer- ence Example | R1 | NMR or Ms |
|---------------------------|--|--|
| 396 | 4-ClPh- | ^1H NMR (CDCl_3) δ 1.87-2.01 (2H, m), 2.04-2.16 (2H, m), 2.91-3.02 (2H, m), 3.29-3.39 (2H, m), 4.34-4.44 (1H, m), 4.85 (1H, s), 6.71-6.78 (2H, m), 6.82-6.92 (4H, m), 7.20-7.26 (2H, m). |
| 397 | 4-CF ₃ Ph- | ^1H NMR (CDCl_3) δ 1.90-2.05 (2H, m), 2.08-2.20 (2H, m), 2.94-3.05 (2H, m), 3.30-3.40 (2H, m), 4.46-4.56 (1H, m), 4.64 (1H, s), 6.72-6.80 (2H, m), 6.86-6.93 (2H, m), 6.96-7.00 (2H, m), 7.52-7.56 (2H, m). |
| 398 | 4-FPh- | ^1H NMR (CDCl_3) δ 1.86-2.00 (2H, m), 2.04-2.16 (2H, m), 2.90-3.00 (2H, m), 3.30-3.40 (2H, m), 4.29-4.39 (1H, m), 4.72 (1H, s), 6.71-6.78 (2H, m), 6.83-7.01 (6H, m). |
| 399 | 4-CH ₃ OPh- | ^1H NMR (CDCl_3) δ 1.86-2.00 (2H, m), 2.05-2.13 (2H, m), 2.88-2.99 (2H, m), 3.31-3.41 (2H, m), 3.77 (3H, s), 4.25-4.35 (1H, m), 4.72 (1H, s), 6.72-6.77 (2H, m), 6.80-6.92 (6H, m). |
| 400 | 4-CH ₃ Ph- | ^1H NMR (CDCl_3) δ 1.87-2.01 (2H, m), 2.04-2.16 (2H, m), 2.29 (3H, s), 2.90-3.00 (2H, m), 3.30-3.40 (2H, m), 4.33-4.43 (1H, m), 4.85 (1H, s), 6.71-6.78 (2H, m), 6.80-6.92 (4H, m), 7.06-7.10 (2H, m). |
| 401 | -C ₆ H ₅ | ^1H NMR (CDCl_3) δ 1.89-2.03 (2H, m), 2.04-2.18 (2H, m), 2.92-3.02 (2H, m), 3.31-3.41 (2H, m), 4.39-4.49 (1H, m), 4.92 (1H, s), 6.70-6.78 (2H, m), 6.84-6.98 (5H, m), 7.24-7.33 (2H, m). |
| 402 | 4-CNPh- | ^1H NMR (CDCl_3) δ 1.90-2.04 (2H, m), 2.09-2.18 (2H, m), 2.94-3.04 (2H, m), 3.29-3.39 (2H, m), 4.49-4.55 (1H, m), 6.75-6.80 (2H, m), 6.86-6.90 (2H, m), 6.93-7.00 (2H, m), 7.55-7.62 (2H, m). |
| 403 | -CH ₂ -cyclo-C ₆ H ₁₁ | Ms: 289 (M ⁺) |
| 404 | | ^1H NMR (CDCl_3) δ 1.54-2.07 (11H, m), 2.74-2.87 (2H, m), 3.31-3.43 (2H, m), 3.47-3.57 (1H, m), 3.72-3.83 (1H, m), 3.88-3.98 (1H, m), 4.74-4.78 (1H, m), 6.69-6.76 (2H, m), 6.83-6.88 (2H, m). |

Table 9



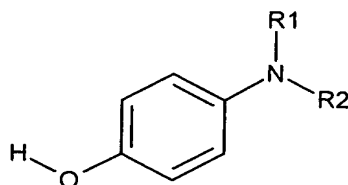
| Refer- ence Example | R1 | R2 | NMR |
|---------------------------|--|--|--|
| 405 | -CH ₃ | 4-CF ₃ OPh- | ¹ H NMR (CDCl ₃) δ 3.23(3H, s), 4.88(1H, s), 6.66-6.73(2H, m), 6.80-6.87(2H, m), 6.99-7.08(4H, m). |
| 406 | -CH ₃ | 4-ClPh- | ¹ H NMR (CDCl ₃) δ 3.22(3H, s), 4.69(1H, brs), 6.66-6.68(2H, m), 6.81-6.84(2H, m), 7.01-7.04(2H, m), 7.10-7.13(2H, m). |
| 407 | -CH ₃ | 4-CF ₃ Ph- | ¹ H NMR (CDCl ₃) δ 3.28(3H, s), 4.80(1H, brs), 6.68-6.71(2H, m), 6.85-6.88(2H, m), 7.06-7.09(2H, m), 7.37-7.40(2H, m). |
| 408 | -C ₂ H ₅ | 4-CF ₃ OPh- | ¹ H NMR (CDCl ₃) δ 1.19(3H, t, J=7.1Hz), 3.66(2H, q, J=7.1Hz), 4.75(1H, brs), 6.62-6.66(2H, m), 6.83-6.87(2H, m), 6.98-7.05(4H, m). |
| 409 | 4-CF ₃ OPhCH ₂ - | 4-CF ₃ OPhCH ₂ - | ¹ H NMR (CDCl ₃) δ 4.34(1H, bs), 4.49(4H, brs), 6.61-6.72(4H, m), 7.14-7.16(4H, m), 7.24-7.26(4H, m). |
| 410 | -C ₂ H ₅ | 4-CF ₃ Ph- | ¹ H NMR (CDCl ₃) δ 1.21(3H, t, J=7.1Hz), 3.70(2H, q, J=7.1Hz), 4.87(1H, brs), 6.62-6.65(2H, m), 6.85-6.91(2H, m), 7.03-7.09(2H, m), 7.34-7.37(2H, m). |
| 411 | -C ₂ H ₅ | 4-ClPh- | ¹ H NMR (CDCl ₃) δ 1.17(3H, t, J=7.1Hz), 3.65(2H, q, J=7.1Hz), 4.73(1H, brs), 6.59-6.63(2H, m), 6.82-6.85(2H, m), 6.98-7.03(2H, m), 7.06-7.10(2H, m). |
| 412 | -CH ₃ | 4-CF ₃ OPhCH ₂ - | ¹ H NMR (CDCl ₃) δ 2.90(3H, s), 4.33(1H, brs), 4.40(2H, brs), 6.66-6.70(2H, m), 6.72-6.76(2H, m), 7.13-7.16(2H, m), 7.25-7.27(2H, m). |
| 413 | -CH ₃ | 4-ClPhCH ₂ - | ¹ H NMR (CDCl ₃) δ 2.88(3H, s), 4.34(1H, brs), 4.36(2H, brs), 6.65-6.69(2H, m), 6.71-6.76(2H, m), 7.15-7.18(2H, m), 7.25-7.28(2H, m). |
| 414 | -CH ₃ | 4-CF ₃ PhCH ₂ - | ¹ H NMR (CDCl ₃) δ 2.92(3H, s), 4.35(1H, brs), 4.46(2H, brs), 6.65-6.68(2H, m), 6.73-6.76(2H, m), 7.34-7.37(2H, m), 7.55-7.58(2H, m). |
| 415 | -C ₂ H ₅ | 4-CF ₃ OPhCH ₂ - | ¹ H NMR (CDCl ₃) δ 1.14(3H, t, J=7.1Hz), 4.12(2H, q, J=7.1Hz), 4.28(1H, brs), 4.39(2H, brs), 6.50-6.80(4H, m), 7.13-7.15(2H, m), 7.26-7.28(2H, m). |
| 416 | -C ₂ H ₅ | 4-CF ₃ PhCH ₂ - | ¹ H NMR (CDCl ₃) δ 1.16(3H, t, J=7.0Hz), 3.38(2H, brs), 4.29(1H, brs), 4.45(2H, brs), 6.61-6.70(4H, m), 7.35-7.38(2H, m), 7.54-7.56(2H, m). |
| 417 | -C ₂ H ₅ | 4-ClPhCH ₂ - | ¹ H NMR (CDCl ₃) δ 1.14(3H, t, J=7.0Hz), 3.35(2H, brs), 4.28(1H, brs), 4.36(2H, brs), 6.62-6.70(4H, m), 7.17-7.19(2H, m), 7.25-7.28(2H, m). |
| 418 | -COCH ₃ | -C ₆ H ₅ | ¹ H NMR (CDCl ₃) δ 2.06(3H, s), 6.27(1H, brs), 6.69-6.80(2H, m), 7.08-7.33(7H, m). |
| 419 | -COCH ₃ | 4-ClPh- | ¹ H NMR (CDCl ₃) δ 2.06(3H, s), 6.50(1H, brs), 6.63-6.85(2H, m), 7.05-7.08(2H, m), 7.18-7.38(4H, m). |

Table 10



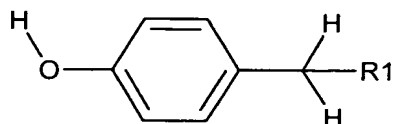
| Refer- ence Example | R1 | R2 | R3 | NMR |
|---------------------------|----------------------------------|--------------------------------|----|---|
| 420 | -CH ₃ | 4-CF ₃ OPh- | -F | ¹ H NMR (CDCl ₃) δ 3.22 (3H, s), 5.02 (1H, brs), 6.57-6.71 (4H, m), 7.01-7.14 (3H, m). |
| 421 | -CH ₃ | 4-ClPh- | -F | ¹ H NMR (CDCl ₃) δ 3.20 (3H, s), 5.02 (1H, brs), 6.54-6.70 (4H, m), 7.07-7.13 (3H, m). |
| 422 | -CO ₂ CH ₃ | -C ₆ H ₅ | -H | ¹ H NMR (CDCl ₃) δ 3.75 (3H, s), 5.86 (1H, brs), 6.69-6.72 (2H, m), 7.05-7.08 (2H, m), 7.18-7.31 (5H, m). |
| 423 | -CO ₂ CH ₃ | 4-ClPh- | -H | ¹ H NMR (CDCl ₃) δ 3.75 (3H, s), 5.52 (1H, brs), 6.73-6.76 (2H, m), 7.04-7.07 (2H, m), 7.16-7.18 (2H, m), 7.26-7.29 (2H, m). |
| 424 | -COCH ₃ | 4-CF ₃ Ph- | -H | ¹ H NMR (CDCl ₃) δ 2.08 (3H, s), 6.04 (1H, brs), 6.83-6.86 (2H, m), 7.09-7.12 (2H, m), 7.37-7.40 (2H, m), 7.56-7.59 (2H, m). |
| 425 | -COCH ₃ | 4-CF ₃ OPh- | -H | ¹ H NMR (CDCl ₃) δ 2.07 (3H, s), 6.60-6.92 (3H, m), 6.98-7.30 (6H, m). |
| 426 | -CH ₃ | -C ₆ H ₅ | -H | ¹ H NMR (CDCl ₃) δ 3.24 (3H, s), 4.63 (1H, brs), 6.76-6.84 (5H, m), 7.01-7.05 (2H, m), 7.17-7.22 (2H, m). |
| 427 | -COCH ₃ | 4-ClPh- | -F | ¹ H NMR (CDCl ₃) δ 2.07 (3H, brs), 6.46-6.61 (2H, m), 6.96-7.36 (6H, m). |
| 428 | -COCH ₃ | 4-CF ₃ OPh- | -F | ¹ H NMR (CDCl ₃) δ 2.07 (3H, brs), 6.48-6.62 (2H, m), 6.90-7.42 (6H, m). |

Table 11



| Refer- ence Example | R1 | R2 | NMR or Ms |
|---------------------------|-------------------------|--|---|
| 429 | $-\text{C}_6\text{H}_5$ | $4-\text{CF}_3\text{OPhCH}_2-$ | ^1H NMR (CDCl_3) δ 4.72(1H, brs), 4.89(2H, brs), 6.75-6.83(5H, m), 7.05-7.18(6H, m), 7.34-7.37(2H, m). |
| 430 | $-\text{C}_6\text{H}_5$ | $4-\text{CF}_3\text{PhCH}_2-$ | ^1H NMR (CDCl_3) δ 4.67(1H, brs), 4.95(2H, brs), 6.74-6.83(5H, m), 7.06-7.18(4H, m), 7.44-7.47(2H, m), 7.54-7.57(2H, m). |
| 431 | $-\text{C}_6\text{H}_5$ | $4-\text{ClPhCH}_2-$ | ^1H NMR (CDCl_3) δ 4.64(1H, brs), 4.86(2H, brs), 6.74-6.82(5H, m), 7.04-7.08(2H, m), 7.12-7.17(2H, m), 7.26(4H, brs). |
| 432 | $-\text{COCH}_3$ | $4-\text{CF}_3\text{OPhCH}_2-$ | ^1H NMR (CDCl_3) δ 1.89(3H, s), 4.83(2H, s), 6.54(1H, brs), 6.82(4H, m), 7.09-7.12(2H, m), 7.20-7.26(2H, m). |
| 433 | $-\text{CH}_3$ | $4-\text{CF}_3\text{PhCO}-$ | ^1H NMR (CDCl_3) δ 3.46(3H, s), 6.28(1H, brs), 6.68-6.71(2H, m), 6.85-6.92(2H, m), 7.33-7.44(4H, m). |
| 434 | $-\text{CH}_3$ | $4-\text{ClPhCO}-$ | ^1H NMR (CDCl_3) δ 3.44(3H, s), 5.12(1H, brs), 6.67-6.72(2H, m), 6.88-6.91(2H, m), 7.13-7.16(2H, m), 7.21-7.24(2H, m). |
| 435 | $-\text{H}$ | $4-\text{CF}_3\text{OPhCO}-$ | ^1H NMR (CDCl_3) δ 6.71-6.76(2H, m), 7.48-7.52(4H, m), 8.02-8.05(2H, m), 9.25(1H, s), 10.10(1H, brs). |
| 436 | $-\text{CH}_3$ | $4-\text{CF}_3\text{OPhCO}-$ | ^1H NMR (CDCl_3) δ 3.45(3H, s), 6.13(1H, brs), 6.69-6.72(2H, m), 6.87-6.89(2H, m), 6.99-7.02(2H, m), 7.31-7.34(2H, m). |
| 437 | $-\text{CH}_3$ | $4-\text{CF}_3\text{OPhO}(\text{CH}_2)_3-$ | ^1H NMR (CDCl_3) δ 1.97-2.06(2H, m), 2.85(3H, s), 3.42(2H, t, $J=6.9\text{Hz}$), 3.99(2H, t, $J=6.0\text{Hz}$), 4.28(1H, brs), 6.65-6.75(4H, m), 6.86-6.89(2H, m), 7.11-7.14(2H, m). |
| 438 | $-\text{H}$ | | 219 ($\text{M}^+ - 1$) |

Table 12



| Reference Example | R1 | NMR or Ms |
|----------------------|----|---|
| 439 | | Ms: 367 (M+) |
| 440 | | ¹ H NMR (CDCl ₃) δ 2.96 (3H, s), 4.43 (2H, brs), 4.68 (1H, s), 6.63–6.66 (2H, m), 6.76–6.80 (2H, m), 7.05–7.08 (2H, m), 7.12–7.15 (2H, m). |
| 441 | | ¹ H NMR (CDCl ₃) δ 1.90 (3H, brs), 4.83 (2H, s), 5.88 (1H, brs), 6.74–6.76 (2H, m), 7.02–7.06 (2H, m), 7.10–7.13 (2H, m), 7.60–7.63 (2H, m). |
| 442 | | ¹ H NMR (CDCl ₃) δ 3.06 (3H, s), 4.52 (2H, s), 4.70 (1H, s), 6.71–6.81 (4H, m), 7.05–7.07 (2H, m), 7.41–7.44 (2H, m). |
| 443 | | ¹ H NMR (CDCl ₃) δ 2.99 (3H, s), 4.44 (2H, s), 4.68 (1H, s), 6.66–6.70 (2H, m), 6.77–6.81 (2H, m), 7.04–7.10 (4H, m). |
| 444 | | ¹ H NMR (CDCl ₃) δ 3.95 (1H, brs), 4.21 (2H, s), 4.69 (1H, brs), 6.53–6.56 (2H, m), 6.79–6.82 (2H, m), 7.09–7.12 (2H, m), 7.20–7.23 (2H, m). |
| 445 | | ¹ H NMR (CDCl ₃) δ 4.28 (3H, brs), 4.71 (1H, brs), 6.60–6.63 (2H, m), 6.79–6.83 (2H, m), 7.21–7.23 (2H, m), 7.38–7.40 (2H, m). |
| 446 | | ¹ H NMR (CDCl ₃) δ 2.16 (3H, s), 3.45 (2H, s), 3.48 (2H, s), 4.82 (1H, brs), 6.76–6.79 (2H, m), 7.14–7.22 (4H, m), 7.35–7.38 (2H, m). |
| 447 | | ¹ H NMR (CDCl ₃) δ 4.03 (1H, brs), 4.22 (2H, s), 4.72 (1H, brs), 6.56–6.69 (2H, m), 6.80–6.83 (2H, m), 7.01–7.04 (2H, m), 7.21–7.24 (2H, m). |

Example 1

Preparation of 2-chloro-1-(3-chloro-2-hydroxypropyl)-4-nitroimidazole

Sodium hydrogencarbonate (1.25 g, 14.91 mmol) was added to a solution of 2-chloro-4-nitro-1H-imidazole (2 g, 13.56 mmol) and epichlorohydrin (1.38 g, 14.91 mmol) in acetonitrile (60 ml), and the resulting mixture was stirred under reflux for 4 hours. The reaction mixture was allowed to return to room temperature, and concentrated under reduced pressure. To the residue, water (20 ml) was added, the resulting mixture was extracted with methylene chloride (15 ml) twice, and the extracts were dried over sodium sulfate, and then filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to afford 2-chloro-1-(3-chloro-2-hydroxypropyl)-4-nitroimidazole (2.04 g, yield 63%) as a light yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:
3.51 - 3.70 (2H, m), 4.02 - 4.35 (4H, m), 7.92 (1H, s).

Example 2

Preparation of 2-chloro-4-nitro-1-(oxiran-2-ylmethyl)-imidazole

2-Chloro-1-(3-chloro-2-hydroxypropyl)-4-nitroimidazole prepared in Example 1 (2.04 g, 8.5 mmol) was dissolved in methylene chloride (20 ml), and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (2.04 ml, 13.67

mmol) was added to the solution. The resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with 3N hydrochloric acid (20 ml) and a saturated saline solution (20 ml) in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford 2-chloro-4-nitro-1-(oxiran-2-ylmethyl)imidazole (190 mg, yield 11%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.55 - 2.69 (1H, m), 2.97 (1H, t, $J = 4.2$ Hz), 3.26 - 3.43 (1H, m), 3.94 (1H, dd, $J = 6.4$ Hz, 15.0 Hz), 4.52 (1H, dd, $J = 2.6$ Hz, 15.0 Hz), 7.88 (1H, s).

Example 3

Preparation of 2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole

2-Chloro-4-nitro-1H-imidazole (6.78 g, 46 mmol) and 2-methyloxiran-2-ylmethyl 4-nitrobenzoate (12 g, 51 mmol) were dissolved in ethyl acetate (24 ml), and triethylamine (1.3 ml, 9.2 mmol) was added to the solution. The resulting mixture was stirred under reflux for 14 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride (40 ml) was added to the residue. The resulting precipitates were filtered off, and dissolved in methanol (120 ml). To the solution, potassium

carbonate (318 mg, 2.3 mmol) was added, and the resulting mixture was stirred at room temperature for 1 hour. To the resulting mixture, 6 N hydrochloric acid (0.8 ml) and magnesium sulfate (8 g) were added in this order with cooling on ice-bath, and the resulting mixture was stirred for 30 minutes. Insoluble matters were removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. To the residue, ethyl acetate (6 ml) and toluene (60 ml) were added. The resulting precipitates were filtered off and dried at 50°C to afford 2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole (7.88 g, yield 72%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, s), 3.25 (2H, d, J = 5.3 Hz), 4.04 (2H, s), 4.98 (1H, s), 5.10 (1H, t, J = 5.4 Hz), 8.29 (1H, s).

Example 4

Preparation of 2-chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole

Methanesulfonyl chloride (2.01 ml, 25.72 mmol) was added to a solution of 2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 3 (5.05 g, 21.43 mmol) in pyridine (10 ml) with cooling on ice-bath and the resulting mixture was stirred at room temperature for 1.5 hours. 6N hydrochloric acid was added to the mixture, and the resulting mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, and

then concentrated under reduced pressure to afford 2-chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole (6.72 g, quantitative) as a yellow oil.

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.31 (3H, s), 2.10 (1H, s), 3.11 (3H, s), 4.08 - 4.23 (4H, m), 8.02 (1H, s).

Example 5

Preparation of 2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole
10 2-Chloro-4-nitro-1H-imidazole (1 g, 6.78 mmol), 2-methyloxiran-2-ylmethyl paratoluenesulfonate (2.46 g, 10.15 mmol), benzyl(triethyl) ammonium chloride (1.50 mg, 0.66 mmol) and acetonitrile (10 ml)
15 were stirred under reflux for 8 hours. The reaction mixture was allowed to return to room temperature, diluted with ethyl acetate. The organic phase was washed with a saturated aqueous sodium bicarbonate solution twice, dried over magnesium sulfate and then
20 filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 6/1) to afford 2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole (1.86
25 g, yield 70%) as a light yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.25 (3H, s), 2.46 (3H, s), 2.80 (1H, s), 3.91 (1H, d, $J = 10.4$ Hz), 3.95 (1H, d, $J = 10.4$ Hz), 4.04 - 4.16

(2H, m), 7.38 (2H, d, $J = 8.0$ Hz), 7.76 (2H, d, $J = 8.0$ Hz), 7.93 (1H, s).

Example 6

Preparation of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-
5 4-nitroimidazole

2-Chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole prepared in Example 4 (6.72 g, 21.43 mmol) was treated in the same manner as in Example 2 to afford 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (5.6 g, yield 94%) as a
10 white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.39 (3H, s), 2.62 (2H, d, $J = 4.0$ Hz), 2.78 (1H, d, $J = 4.0$ Hz), 4.00 (1H, d, $J = 14.9$ Hz), 4.38 (1H, d, $J =$
15 14.9 Hz), 7.87 (1H, s).

Example 7

Preparation of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-
4-nitro-1H-imidazole

Using 2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole
20 prepared in Example 5 (1.11 g, 2.84 mmol) gave 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitro-1H-imidazole (523 mg, yield 85%) as a light yellow powder in the same manner as in Example 2.

25 The properties of the obtained compound were same as those of the compound obtained in Example 6.

Example 8

Preparation of (R)-2-chloro-1-[2-hydroxy-3-(4-

methylbenzenesulfonyloxy)propyl]-4-nitroimidazole

2-Chloro-4-nitro-1H-imidazole (10 g, 67.79 mmol) and (R)-(-)-glycidyl tosylate (17.02 g, 74.58 mmol) were dissolved in acetonitrile (50 ml), sodium hydrogencarbonate (6.26 g, 74.15 mmol) was added to the solution, and the resulting mixture was stirred under reflux for 3.5 hours. The reaction mixture was allowed to return to room temperature. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to afford (R)-2-chloro-1-[2-hydroxy-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole (16.9 g, yield 66%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

2.47 (3H, s), 3.65 (1H, d, J = 5.8 Hz), 3.93 - 4.33 (5H, m), 7.38 (2H, d, J = 8.3 Hz), 7.70 (2H, d, J = 8.3 Hz), 7.86 (1H, s).

Example 9

Preparation of (R)-2-chloro-4-nitro-1-(oxiran-2-yl-methyl)imidazole

2-Chloro-4-nitro-1H-imidazole (1 g, 6.78 mmol) and (R)-(-)-glycidyl tosylate (1.7 g, 7.45 mmol) were dissolved in tetrahydrofuran (THF) (10 ml), sodium hydrogencarbonate (600 mg, 7.14 mmol) was added to the solution, and the resulting mixture was stirred under reflux for 11 hours. The reaction mixture was concentrated under reduced pressure, water was added to

the solution, and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with water and a saturated saline solution in this order, dried over sodium sulfate, and filtered. The filtrate
 5 was concentrated, and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to afford (R)-2-chloro-4-nitro-1-(oxiran-2-ylmethyl)imidazole (1.45 g, yield 57%) as a light yellow oil.

10 Optical purity 79.2% e.e.
 $[\alpha]_D^{27} = 42.55^\circ$ (concentration: 1.262, CHCl_3)
 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
 2.61 (1H, t, $J = 2.5 \text{ Hz}$, 4.3 Hz), 2.97 (1H, t, $J = 4.3 \text{ Hz}$), 3.25 - 3.34 (1H, m), 3.95 (1H, dd, $J = 6.4 \text{ Hz}$,
 15 15.0 Hz), 4.51 (1H, dd, $J = 2.6 \text{ Hz}$, 15.0 Hz), 7.88 (1H, s).

Example 10

Preparation of (R)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole

20 2-Chloro-4-nitro-1H-imidazole (600 g, 4.07 mol) and (R)-2-methyloxiran-2-ylmethyl 4-nitrobenzoate (1060 g, 4.47 mol) were dissolved in ethyl acetate (2124 ml), triethylamine (113.64 ml, 0.82 mol) was added to the solution, and the resulting mixture was
 25 stirred under reflux for 16 hours. The reaction mixture was concentrated under reduced pressure, and ethyl acetate (530 ml) and toluene (5300 ml) were added to the residue. The resulting precipitates were

filtered off and dissolved in methanol (10.6 l). Potassium carbonate (55.4 g, 0.4 mol) was added to the solution, the resulting mixture was stirred at room temperature for 1 hour, concentrated hydrochloric acid (66 ml) and magnesium sulfate (671 g) were added in this order with cooling on ice-bath, and the resulting mixture was stirred for 30 minutes. Insoluble matters were removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue, ethyl acetate (530 ml) and toluene (5300 ml) were added. The resulting precipitates were filtered off and dried at 50°C to afford (R)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole (879.1 g, yield 92%) as a light brown powder.

Optical purity 99.0% e.e.

$[\alpha]_D^{27} = 17.38^\circ$ (concentration: 1.03, DMSO)

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm:

1.01 (3H, s), 3.25 (2H, d, $J = 5.3$ Hz), 4.05 (2H, s), 5.01 (1H, s), 5.11 (1H, t, $J = 5.4$ Hz), 8.32 (1H, s).

Example 11

Preparation of (R)-2-chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole

(R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (879 g, 3.73 mol) was dissolved in pyridine (1778 ml) and cooled to 5°C. To this solution, methanesulfonyl chloride (432.7 ml, 5.59 mol) was added dropwise below 15°C, and the resulting mixture was stirred at the same

temperature for 1 hour. To the mixture, 6N hydrochloric acid (5500 ml) was added below 30°C, and the resulting mixture was stirred for 40 minutes with cooling on ice-bath. The precipitates were filtered off and washed with water and toluene in this order to afford primary crystals. In addition, the filtrate was extracted with ethyl acetate (5 liters) twice. The organic phase was washed with water, dried over magnesium sulfate, and filtered to afford a solid. The filtrate was concentrated under reduced pressure. To the residue, toluene was added and the precipitates were filtered off to afford a solid. The solids were combined and dried at 60°C to afford (R)-2-chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole (942.6 g, yield 81%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:
1.12 (3H, s), 3.23 (3H, s), 4.09 (2H, s), 4.13 (2H, s), 5.60 (1H, br), 8.34 (1H, s).

Example 12

Preparation of (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole

(R)-2-Chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole prepared in Example 11 (942.6 g, 3 mol) was suspended in ethyl acetate (9426 ml). DBU (494 ml, 3.3 mol) was added to the suspension, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was washed with water (5 liters). The water layer was

extracted with ethyl acetate (5 liters) twice. The organic phases were combined together, and the mixture was washed with a saturated saline solution (5 liters), dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to afford (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (600.7 g, yield 92%) as a white powder.

Optical purity 98.8% e.e.

$[\alpha]_D^{26} = 31.11^\circ$ (concentration: 2.02, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.38 (3H, s), 2.62 (1H, d, $J = 4.0$ Hz), 2.78 (1H, d, $J = 4.0$ Hz), 4.00 (1H, d, $J = 14.9$ Hz), 4.38 (1H, d, $J = 14.9$ Hz), 7.87 (1H, s).

Example 13

Preparation of (R)-2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole

2-Chloro-4-nitro-1H-imidazole (18.4 g, 125 mmol) and (R)-2-methyloxiran-2-ylmethyl 4-methylbenzene sulfonate (36.2 g, 149 mmol) were suspended in acetonitrile (150 ml). Benzyl(triethyl) ammonium chloride (5.7 g, 25 mmol) was added to the suspension, and the resulting mixture was stirred under reflux for 8 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford (R)-2-chloro-1-[2-hydroxy-2-

methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole (20.1 g, 43%) as a white amorphous form.

^1H -NMR (CDCl_3) δ ppm:

1.24 (3H, s), 2.47 (3H, s), 2.81 (1H, s), 3.90 (1H, d, J = 10.4 Hz), 3.95 (1H, d, J = 10.4 Hz), 4.04 - 4.14 (2H, m), 7.39 (2H, d, J = 8.0 Hz), 7.76 (2H, d, J = 8.0 Hz), 7.91 (1H, s).

Example 14

Preparation of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (another method for synthesis of the compound of Example 12)

2-Chloro-4-nitro-1H-imidazole (1.51 g, 10.17 mmol) and (R)-2-methyloxiran-2-ylmethyl 4-methylbenzene sulfonate (3.70 g, 15.25 mmol) were suspended in acetonitrile (150 ml). Benzyl(triethyl) ammonium chloride (0.23, 1.02 mmol) was added to this suspension, and the resulting mixture was stirred under reflux for 10 hours. After the reaction mixture was allowed to return to room temperature, ethyl acetate was added to the solution. The resulting mixture was washed with an aqueous sodium hydrogencarbonate, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure and dissolved in ethyl acetate (40 ml). DBU (1.57 ml, 10.17 mmol) was added to the solution with cooling on ice-bath, and the resulting mixture was stirred at room temperature for 1.5 hours. The reaction mixture was washed with water, dried over magnesium sulfate, and then concen-

trated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 7/3) to afford (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (1.50 g, 5 yield 68%) as a light yellow oil.

Example 15

Preparation of (S)-2-chloro-4-nitro-1-[2-hydroxy-3-(4-nitrobenzoyloxy)-2-methylpropyl]imidazole

2-Chloro-4-nitro-1H-imidazole (3 g, 20.34 10 mmol) and (S)-2-methyloxiran-2-ylmethyl 4-nitrobenzoate (5.31 g, 22.37 mmol) were dissolved in ethyl acetate (10 ml). Triethylamine (0.57 ml, 4.07 mmol) was added to the solution, and the resulting mixture was stirred at 60-65°C for 10 hours. The reaction mixture was 15 concentrated under reduced pressure. Ethyl acetate (3 ml) and toluene (30 ml) were added to the residue, and the resulting precipitates were filtered off to afford (S)-2-chloro-4-nitro-1-[2-hydroxy-3-(4-nitrobenzoyloxy)-2-methylpropyl]imidazole (6.82 g, 20 yield 87%) as a yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.23 (3H, s), 4.11 - 4.33 (4H, m), 5.61 (1H, s), 8, 25 (2H, d, J = 8.9 Hz), 8.31 - 8.45 (3H, m).

25 Example 16

Preparation of (S)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole

(S)-2-Chloro-4-nitro-1-[2-hydroxy-3-(4-

nitrobenzoyloxy)-2-methylpropyl]imidazole prepared in Example 15 (6.8 g, 17.67 mmol) was dissolved in methanol (68 ml). Potassium carbonate (122 mg, 0.88 mmol) was added to the solution, and the resulting mixture was stirred at room temperature overnight. The mixture was cooled on ice-bath, 6N hydrochloric acid (0.3 ml) and magnesium sulfate (3 g) were added to the mixture in this order, and the mixture was stirred for 30 minutes. Insoluble matters were removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl acetate (3.4 ml) and toluene (34 ml) were added to the residue, and the resulting precipitates were filtered off to afford (S)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole (4.09 g, yield 97%) as a yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, s), 3.25 (2H, d, J = 5.3 Hz), 4.05 (2H, s), 4.98 (1H, s), 5.11 (1H, t, J = 5.2 Hz), 8.30 (1H, s).

Example 17

Preparation of (S)-2-chloro-1-(2-hydroxy-2-methyl-3-methanesulfonyloxypropyl)-4-nitroimidazole

(S)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 16 (4.05 g, 16.9 mmol) was dissolved in pyridine (8 ml), and this solution was cooled to 4°C. Methanesulfonyl chloride (1.6 ml, 20.28 mmol) was added dropwise to the solution below 15°C followed by stirring at the same temperature for 1 hour. 6N hydrochloric acid (33 ml)

was added to the mixture below 30°C. The reaction mixture was extracted with methylene chloride (20 ml) three times. The organic phases were combined, washed with water (20 ml) and a saturated saline solution (20 ml), dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. Toluene (10 ml) was added to the residue, and the resulting precipitates were filtered off to afford (S)-2-chloro-1-(2-hydroxy-2-methyl-3-methanesulfonyloxypropyl)-4-nitroimidazole (3.04g, yield 57%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:

1.12 (3H, s), 3.24 (3H, s), 4.09 (2H, s), 4.13 (2H, s), 5.62 (1H, br), 8.34 (1H, s).

Example 18

Preparation of (S)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole

(S)-2-Chloro-1-(2-hydroxy-2-methyl-3-methanesulfonyloxypropyl)-4-nitroimidazole prepared in Example 17 (3.02 g, 9.51 mmol) was dissolved in methylene chloride (30 ml). DBU (1.7 ml, 11.41 mmol) was added to the solution, and the resulting mixture was stirred at room temperature for 1.5 hours. The reaction mixture was washed with 3N hydrochloric acid (30 ml) and saturated saline solution (20 ml) in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (methylene

chloride/ethyl acetate = 20/1) to afford (S)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (1.89 g, yield 91%) as a light yellow solid.

Optical purity 93.2% e.e.

5 $[\alpha]_D^{27} = -29.15^\circ$ (concentration: 1.18, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.39 (3H, s), 2.63 (1H, d, $J = 4.0$ Hz), 2.79 (1H, d, $J = 4.0$ Hz), 4.00 (1H, d, $J = 14.9$ Hz), 4.38 (1H, d, $J = 14.9$ Hz), 7.88 (1H, s).

10 Example 19

Preparation of 2-tert-butoxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

2,4-Dinitro-1H-imidazole (10 g, 63.3 mmol), 2-tert-butoxymethyloxirane (27 ml, 189 mmol) and sodium acetate (5.19 g, 189 mmol) were suspended in ethanol (100 ml) followed by stirring under reflux for 17 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 2-tert-butoxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (3.2 g, yield 21%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.18 (9H, s), 3.63 - 3.80 (2H, m), 4.22 - 4.36 (2H, m),
5.27 - 5.42 (1H, m), 7.53 (1H, s).

Using 2-methyl-2-(2-methoxymethoxyethyl)
oxirane, 2-ethyl-2-methoxymethoxymethyloxirane or 2-
5 isopropyl-2-methoxymethoxymethyloxirane gave compounds
of Examples 20 to 22 in the same manner as in Example
19.

Example 20

2-(2-Methoxymethoxyethyl)-2-methyl-6-nitro-2,3-
10 dihydroimidazo[2,1-b]oxazole
White powder, yield 48%, MS = 257

Example 21

2-Ethyl-2-methoxymethoxymethyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole
15 Light yellow powder, yield 49%
¹H-NMR (DMSO-d₆) δppm:
0.91 (3H, t, J = 7.5 Hz), 1.91 (2H, q, J = 7.5 Hz),
3.24 (3H, s), 3.72 (1H, d, J = 11.2 Hz), 3.78 (1H, d, J
= 11.2 Hz), 4.15 (1H, d, J = 11.2 Hz), 4.23 (1H, d, J =
20 11.2 Hz), 4.59 (2H, s), 8.10 (1H, s).

Example 22

2-Isopropyl-2-methoxymethoxymethyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole
Light yellow powder, yield 90%
25 ¹H-NMR (DMSO-d₆) δppm:
0.94 (6H, d, J = 6.9 Hz), 2.16 - 2.32 (1H, m), 3.24
(3H, s), 3.76 (1H, d, J = 13.0 Hz), 3.82 (1H, d, J =
13.0 Hz), 4.18 (1H, d, J = 13.0 Hz), 4.25 (1H, d, J =

13.0 Hz), 4.59 (2H, s), 8.09 (1H, s).

Example 23

Preparation of 2-chloro-1-(2-hydroxy-4-methoxymethoxy-butyl)-4-nitroimidazole

5 Sodium acetate (3.51 g, 42.82 mmol) and 2-(2-methoxymethoxyethyl) oxirane (10.3 g, 77.86 mmol) were added to 2-chloro-4-nitro-1H-imidazole (5.74 g, 38.93 mmol) in ethanol (60 ml), and the resulting mixture was stirred under reflux for 13.5 hours. The reaction
10 mixture was concentrated under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate and then concentrated under reduced pressure, and the residue was purified by
15 silica gel column chromatography (methylene chloride/methanol = 100/1) and then crystallized from methylene chloride-diisopropyl ether to afford 2-chloro-1-(2-hydroxy-4-methoxymethoxybutyl)-4-nitroimidazole (8.51 g, yield 78%) as a light yellow
20 powder.

¹H-NMR (CDCl₃) δppm:

1.67 (2H, m), 3.38 (3H, s), 3.46 (1H, d, J = 2.4 Hz),
3.78 - 3.83 (2H, m), 4.00 (1H, dd, J = 7.6 Hz, 14.3 Hz), 4.11 - 4.21 (2H, m), 4.63 (2H, s), 7.96 (1H, s).

25 Using 2-methyl-2-methoxymethoxymethyloxirane gave a compound of Example 24 in the same manner as in Example 23.

Example 24

2-Chloro-1-(2-hydroxy-3-methoxymethoxypropyl)-4-nitroimidazole

Colorless liquid, yield 63%

¹H-NMR (CDCl₃) δppm:

5 1.20 (3H, s), 3.08 (1H, s), 3.42 (3H, s), 3.53 (2H, dd, J = 10.4 Hz, 13.8 Hz), 4.67 (2H, s), 8.01 (1H, s).

Example 25

Preparation of 2-(2-methoxymethoxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

10 Sodium hydride (1.33 g, 33.23 mmol) was added to a solution of 2-chloro-1-(2-hydroxy-4-methoxymethoxybutyl)-4-nitroimidazole prepared in Example 23 (8.45 g, 30.21 mmol) in 1,4-dioxane (100 ml) with cooling on ice-bath followed by stirring under
15 reflux for 40 hours. The reaction mixture was concentrated under reduced pressure, and cooled on ice-bath. Water was added to the residue, and the resulting mixture was extracted with methylene chloride. The organic phase was dried over magnesium
20 sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford 2-(2-methoxymethoxyethyl)-6-nitro-2,3-
25 dihydroimidazo[2,1-b]oxazole (3.4 g, yield 47%) as a light yellow powder.

¹H-NMR (CDCl₃) δppm:

2.11 - 2.35 (2H, m), 3.36 (3H, s), 3.75 (2H, dd, J =

4.8 Hz, 6.8 Hz), 4.08 (1H, dd, $J = 7.6$ Hz, 10.3 Hz),
 4.40 (1H, dd, $J = 7.6$ Hz, 10.3 Hz), 4.61 (2H, s), 5.43
 - 5.54 (1H, m), 7.53 (1H, s).

Using 2-chloro-1-(2-hydroxy-3-methoxymethoxy-
 5 propyl)-4-nitroimidazole prepared in Example 24 gave a
 compound of Example 26 in the same manner as in Example
 25.

Example 26

2-Methoxymethoxymethyl-2-methyl-6-nitro-2,3-
 10 dihydroimidazo[2,1-b]oxazole

Light yellow powder, yield 38%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.66 (3H, s), 3.34 (3H, s), 3.63 (1H, d, $J = 11.0$ Hz),
 3.84 (1H, d, $J = 11.0$ Hz), 3.93 (1H, d, $J = 9.9$ Hz),
 15 4.37 (1H, d, $J = 9.9$ Hz), 4.62 (2H, s), 7.52 (1H, s).

Example 27

Preparation of (R)-2-chloro-1-(2-hydroxy-3-methoxy-
 methoxy-2-methylpropyl)-4-nitroimidazole

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl-
 20 propyl)-4-nitroimidazole prepared in Example 10 (7.4 g,
 31 mmol) was dissolved in methylene chloride (120 ml).
 N, N-diisopropylethylamine (13.1 ml, 74 mmol) and
 chloromethylmethyl ether (7.1 ml, 74 mmol) were added
 to the solution followed by stirring at room
 25 temperature for 46 hours. The reaction mixture was
 washed with water, dried over magnesium sulfate and
 then concentrated under reduced pressure. The residue
 was purified by silica gel column chromatography

(methylene chloride/ethyl acetate = 9/1) to afford (R)-2-chloro-1-(2-hydroxy-3-methoxymethoxy-2-methylpropyl)-4-nitroimidazole (6.0 g, yield 69%) as a light yellow oil.

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.20 (3H, s), 3.08 (1H, s), 3.42 (3H, s), 3.50 (1H, d, $J = 10.4$ Hz), 3.55 (1H, d, $J = 10.4$ Hz), 4.05 (1H, d, $J = 14.4$ Hz), 4.15 (1H, d, $J = 14.4$ Hz), 4.67 (2H, s), 8.01 (1H, s).

10 Example 28

Preparation of (R)-2-methoxymethoxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Sodium hydride (1.0 g, 25 mmol) was added to a solution of (R)-2-chloro-1-(2-hydroxy-3-methoxymethoxy-2-methylpropyl)-4-nitroimidazole prepared in Example 27 (6.0 g, 21 mmol) in DMF (30 ml) with cooling on ice-bath followed by stirring at room temperature for 1.5 hours. Ice-water was added to the reaction mixture, and the precipitates were filtered off and washed with water to afford (R)-2-methoxymethoxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (3.1 g, yield 59%) as a yellow solid.

25 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.66 (3H, s), 3.34 (3H, s), 3.63 (1H, d, $J = 11.0$ Hz), 3.84 (1H, d, $J = 11.0$ Hz), 3.93 (1H, d, $J = 10.0$ Hz), 4.42 (1H, d, $J = 10.0$ Hz), 4.63 (2H, s), 7.52 (1H, s).

Example 29

Preparation of 2-chloro-1-(5-acetoxy-2-hydroxy-2-methylpentyl)-4-nitroimidazole

2-Chloro-4-nitro-1H-imidazole (6.8 g, 43 mmol), 2-(3-acetoxypropyl)-2-methyloxirane (5.8 g, 39.3 mmol) and sodium acetate (3.9 g, 47.6 mmol) were suspended in ethanol (60 ml) followed by stirring under reflux overnight. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with methylene chloride twice. The organic phases were combined, washed with a saturated aqueous sodium bicarbonate solution and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to afford 2-chloro-1-(5-acetoxy-2-hydroxy-2-methylpentyl)-4-nitroimidazole (9.5 g, yield 79%) as a light brown oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.21 (3H, s), 1.50 - 1.81 (4H, m), 2.05 (3H, s), 3.91 - 4.12 (4H, m), 8.02 (1H, s).

Example 30

Preparation of 2-(3-acetoxypropyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Using 2-chloro-1-(5-acetoxy-2-hydroxy-2-methylpentyl)-4-nitroimidazole (9.5 g, 31.1 mmol) prepared in Example 29 gave 2-(3-acetoxypropyl)-2-

methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (5.2 g, yield 62%) as a light orange-colored powder in the same manner as in Example 25.

¹H-NMR (CDCl₃) δppm:

5 1.67 (3H, s), 1.67 - 2.00 (4H, m), 2.05 (3H, s), 3.91 - 4.14 (4H, m), 7.52 (1H, s).

Example 31

Preparation of 2-(2-hydroxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

10 Trifluoroacetic acid (2 ml) was added to a solution of 2-(2-methoxymethoxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 25 (0.2 g, 0.822 mmol) in methylene chloride (10 ml) followed by stirring at room temperature overnight.

15 The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1), and crystallized from methanol-diisopropyl ether to afford 2-(2-hydroxyethyl)-6-nitro-2,3-

20 dihydroimidazo[2,1-b]oxazole (0.11 g, yield 65%) as a light yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.92 - 2.14 (2H, m), 3.52 - 3.63 (2H, m), 4.05 (1H, dd, J = 7.6 Hz, 10.6 Hz), 4.43 (1H, dd, J = 7.6 Hz, 10.6

25 Hz), 4.72 (1H, t, J = 2.7 Hz), 5.38 - 5.53 (1H, m), 8.12 (1H, s).

Example 32

Preparation of 2-hydroxymethyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazole

Using 2-tert-butoxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 19 (5.82 g, 24.1 mmol) gave 2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (4.25 g, yield 95%) as a white powder in the same manner as in Example 31.

¹H-NMR (DMSO-d₆) δppm:

3.55 - 3.67 (1H, m), 3.72 - 3.88 (1H, m), 4.12 (1H, dd, J = 6.5 Hz, 10.5 Hz), 4.36 (1H, t, J = 10.4 Hz), 5.25 - 5.50 (2H, m), 8.11 (1H, s).

Example 33

Preparation of 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Using 2-methoxymethoxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 26 (4.14 g, 38 mmol) gave 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (2.17 g, yield 64%) as a light yellow powder in the same manner as in Example 31.

Melting point 166-168°C

¹H-NMR (DMSO-d₆) δppm:

1.51 (3H, s), 3.53 (1H, d, J = 12.1 Hz), 3.64 (1H, d, J = 12.1 Hz), 4.03 (1H, d, J = 10.6 Hz), 4.24 (1H, d, J = 10.6 Hz), 5.40 (1H, br), 8.10 (1H, s).

Example 34

Preparation of 2-(2-hydroxyethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Using 2-(2-methoxymethoxyethyl)-2-methyl-6-

nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 20 (13.4 g, 52.1 mmol) gave 2-(2-hydroxyethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (2.32 g, yield 21%) as a light yellow powder in the same manner as in Example 31.

¹H-NMR (DMSO-d₆) δppm:

1.58 (3H, s), 1.93 - 2.17 (2H, m), 3.59 (2H, t, J = 6.4 Hz), 4.04 (1H, d J = 10.9 Hz), 4.33 (d, 1H, J = 10.9 Hz), 8.11 (1H, s).

10 Example 35

Preparation of 2-ethyl-2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

2-Ethyl-2-methoxymethoxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 21 (21.5 g, 83.7 mmol) was suspended in methanol (430 ml). Concentrated hydrochloric acid (2.15 ml) was added to this suspension followed by stirring under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the precipitates were filtered off to afford 2-ethyl-2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (7.14 g, yield 40%) as a light yellow powder.

¹H-NMR (DMSO-d₆) δppm:

0.89 (3H, t, J = 7.4 Hz), 1.95 (2H, q, J = 7.4 Hz), 3.53 - 3.69 (2H, m), 4.08 (1H, d, J = 10.8 Hz), 4.21 (1H, d, J = 10.8 Hz), 5.39 (t, 1H, J = 5.6 Hz), 8.09 (1H, s).

Using corresponding starting materials gave a

compound of Example 36 in the same manner as in Example 35.

Example 36

2-Hydroxymethyl-2-isopropyl-6-nitro-2,3-dihydro-

5 imidazo[2,1-b]oxazole

Light yellow powder, yield 50%

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm:

0.91 (6H, d, $J = 6.9$ Hz), 2.12 - 2.23 (1H, m), 3.60 -
3.77 (2H, m), 4.16 (2H, s), 5.35 (1H, t, $J = 5.6$ Hz),

10 8.08 (1H, s).

Example 37

Preparation of (R)-2-hydroxymethyl-2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazole

Trifluoroacetic acid (15 ml) was added to a
15 solution of (R)-2-methoxymethoxymethyl-2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in
Example 28 (3.1 g, 13 mmol) in methylene chloride (30
ml) followed by stirring at room temperature for 25
hours. The reaction mixture was concentrated under
20 reduced pressure. Methanol was added to the solution,
and the resulting mixture was concentrated under
reduced pressure. To the residue, 2-propanol was
added, and the precipitates were filtered off and
washed with 2-propanol to afford (R)-2-hydroxymethyl-2-
25 methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (1.2 g,
yield 46%) as a light yellow powder.

Melting point 162-163°C

Optical purity 97% e.e.

$[\alpha]_D^{26} = -19.01^\circ$ (concentration: 0.526, DMSO)

Example 38

Preparation of 2-methyl-2-(3-hydroxypropyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

5 A mixture of 2-(3-acetoxypentyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 30 (3.2 g, 11.88 mmol), potassium carbonate (320 mg, 2.32 mmol) and methanol (35 ml) was stirred at room temperature for 2 hours. The reaction mixture was
10 concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 25/1) to afford 2-methyl-2-(3-hydroxypropyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (2.1 g, 78%) as a light
15 yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.67 - 1.72 (5H, m), 1.91 - 2.07 (2H, m), 3.51 - 3.65 (2H, m), 4.01 (1H, d, $J = 10.5$ Hz), 4.15 (1H, d, $J = 10.5$ Hz), 7.66 (1H, s).

20 Example 39

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl methanesulfonate

 Methanesulfonyl chloride (1.4 ml, 18.09 mmol) in methylene chloride (10 ml) was added dropwise to a
25 mixture of 2-methyl-2-(3-hydroxypropyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 38 (2.1 g, 9.24 mmol), triethylamine (2.8 g, 20.09 mmol), 4-dimethylaminopyridine (50 mg, 0.41 mmol) and

methylene chloride (80 ml) with cooling on ice-bath followed by stirring at room temperature overnight.

The reaction mixture was concentrated. 10%

hydrochloric acid was added to the residue, and the

5 resulting mixture was stirred for 30 minutes with cooling on ice-bath. The precipitates were filtered off and washed with water to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl methanesulfonate (2.6 g, yield 92%) as a white powder.

10 ¹H-NMR (DMSO-d₆) δppm:

1.58 (3H, s), 1.65 - 2.02 (4H, m), 3.17 (3H, s), 4.05 - 4.26 (4H, m), 8.12 (1H, s).

Using corresponding starting materials gave compounds of Examples 40 to 42 in the same manner as in

15 Example 39.

Example 40

6-Nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate

Light yellow powder, yield 82%

20 ¹H-NMR (DMSO-d₆) δppm:

3.25 (3H, s), 4.11 (1H, dd, J = 6.6 Hz, 11.0 Hz), 4.47 (1H, t, J = 9.1 Hz), 4.55 - 4.70 (2H, m), 5.60 - 5.75 (1H, m), 8.14 (1H, s).

Example 41

25 2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate

Light yellow powder, yield 87%

¹H-NMR (DMSO-d₆) δppm:

1.64 (3H, s), 3.24 (3H, s), 4.17 (1H, d, J = 11.2 Hz),
4.27 (1H, d, J = 11.2 Hz), 4.52 (2H, br), 8.14 (1H, s).

Example 42

2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
5 yl)ethyl methanesulfonate

Light yellow powder, yield 87%

¹H-NMR (DMSO-d₆) δppm:

1.61 (3H, s), 2.38 (2H, t, J = 6.5 Hz), 3.19 (3H, s),
4.11 (1H, d, J = 11.0 Hz), 4.25 (1H, d, J = 11.0 Hz),
10 4.36 (2H, t, J = 6.5 Hz), 8.14 (1H, s).

Example 43

Preparation of tert-butyl 5-(2-chloro-4-nitroimidazol-
1-yl)-4-hydroxy-4-methylpentanoate

Sodium acetate (0.59 g, 7.18 mmol) was added
15 to a suspension of tert-butyl 3-(2-methyloxiran-2-
yl)propionate (1.00 g, 5.39 mmol) and 2-chloro-4-nitro-
1H-imidazole (0.53 g, 3.59 mmol) in ethanol (5 ml)
followed by stirring under reflux for 6 hours.

Insoluble matters were removed by filtration, and the
20 filtrate was concentrated under reduced pressure. The
residue was purified by silica gel column
chromatography (methylene chloride/methanol = 100/1) to
afford tert-butyl 5-(2-chloro-4-nitroimidazol-1-yl)-4-
hydroxy-4-methylpentanoate (0.94 g, yield 78%) as a
25 light yellow oil.

¹H-NMR (CDCl₃) δppm:

1.17 (3H, s), 1.45 (9H, s), 1.78 - 1.87 (2H, m), 2.43 -
2.54 (2H, m), 3.59 (1H, br), 3.99 (2H, s), 8.06 (1H,

s).

Example 44

Preparation of tert-butyl 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propionate

5 Sodium hydride (0.12 g, 3.07 mmol) was added to a solution of tert-butyl 5-(2-chloro-4-nitroimidazol-1-yl)-4-hydroxy-4-methylpentanoate prepared in Example 43 (0.93 g, 2.79 mmol) in 1,4-dioxane (10 ml) with cooling on ice-bath followed by
10 stirring under reflux for 7.5 hours. The reaction mixture was concentrated under reduced pressure. Water was added to the solution, and the resulting mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then
15 concentrated under reduced pressure. The residue was treated with diethyl ether to afford tert-butyl 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propionate (0.35 g, 42%) as a white solid.

¹H-NMR (CDCl₃) δppm:

20 1.45 (9H, s), 1.65 (3H, s), 2.12 - 2.25 (2H, m), 2.37 - 2.46 (2H, m), 3.98 (1H, d, J = 10.3 Hz), 4.10 (1H, d, J = 10.3 Hz), 7.52 (1H, s).

Example 45

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-
25 [2,1-b]oxazol-2-yl)propionic acid

Trifluoroacetic acid (2 ml) was added to a solution of tert-butyl 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl) propionate prepared

in Example 44 (0.72 g, 2.42 mmol) in methylene chloride (14 ml) followed by stirring at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The residue was crystallized from 5 ethanol-methylene chloride to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propionic acid (0.30 g, 51%) as a light yellow solid.

¹H-NMR (DMSO-d₆) δppm:

1.32 (3H, s), 1.91 - 2.09 (1H, m), 2.12 - 2.26 (1H, m),
10 2.41 - 2.74 (2H, m), 3.89 (2H, s), 7.96 (1H, s), 12.19
(1H, br).

Example 46

Preparation of 2-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethoxy)benzoxazole

15 Sodium hydride (77 mg, 1.9 mmol) was added to a solution of 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 33 (0.32 g, 1.6 mmol) in DMF (3 ml) with cooling on ice-bath followed by stirring at 0°C for 30 minutes. To the
20 reaction mixture, 2-chlorobenzoxazole (0.30 g, 1.9 mmol) in DMF (3 ml) was added with cooling on ice-bath followed by stirring at room temperature for 44 hours. Ice-water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate.
25 The organic phase was washed with water, dried over magnesium sulfate and then concentrated. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and

recrystallized from acetonitrile-isopropanol to afford 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoxazole (0.20 g, 39%) as a light yellow solid.

5 Melting point 200-203°C

Example 47

Preparation of (R)-2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoxazole

Sodium hydride (0.1 g, 2.4 mmol) was added to
10 a solution of (R)-2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 37 (0.40 g, 2.0 mmol) in DMF (4 ml) followed by stirring for 30 minutes with cooling on ice-bath. To the reaction mixture, 2-chlorobenzoxazole (0.38 g, 2.4
15 mmol) in DMF (4 ml) was added with cooling on ice-bath followed by stirring at room temperature for 48 hours. Ice-water was added to the reaction mixture. The precipitates were filtered off, washed with water, and then recrystallized from acetonitrile-isopropanol to
20 afford (R)-2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoxazole (0.15 g, yield 24%) as a light yellow solid.

Melting point 232-233°C

Optical purity > 99.5% e.e.

25 $[\alpha]_D^{26} = +11.20^\circ$ (concentration: 0.518, DMSO)

Example 48

Preparation of 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylthio)benzoxazole

Sodium hydride (50 mg, 1.25 mmol) was added to a mixture of 2-mercaptobenzoxazole (200 mg, 1.3 mmol) and DMF (3 ml) followed by stirring at room temperature for 1 hour. To the reaction mixture, 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate prepared in Example 41 (330 mg, 1.2 mmol) was added, and the resulting mixture was stirred at 60-70°C for 5 hours. The reaction mixture was allowed to return to room temperature. Water was added to the solution, and the resulting mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with 5% sodium hydroxyde solution and water three times, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylthio)benzoxazole (37 mg, yield 9%) as a white powder.

Melting point 163-166°C

Example 49

Preparation of 2-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethylthio]benzoxazole

Using 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl methanesulfonate prepared in Example 42 (300 mg, 1 mmol) gave 2-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethylthio]benzoxazole (296 mg, yield 83%) as a white

powder in the same manner as in Example 48.

Melting point 174-175°C

Example 50

Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(1-phenyl-1H-tetrazol-5-ylthio)propane-2-ol

A mixture of 2-chloro-4-nitro-1H-imidazole (1.2 g, 8.13 mmol), 5-(2-methyloxiran-2-ylmethylthio)-1-phenyl-1H-tetrazole (1.9 g, 7.65 mmol), sodium acetate (700 mg, 8.53 mmol) and ethanol (20 ml) was stirred under reflux overnight. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the resulting mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with a saturated aqueous sodium bicarbonate solution twice, then washed with water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(1-phenyl-1H-tetrazol-5-ylthio)propane-2-ol to afford (2.1 g, yield 69%) as a light yellow powder.

¹H-NMR (CDCl₃) δppm:

1.38 (3H, s), 3.54 (1H, d, J = 14.8 Hz), 3.62 (1H, d, J = 14.8 Hz), 4.19 (2H, s), 4.58 (1H, s), 7.50 - 7.67 (5H, m), 8.08 (1H, s).

Example 51

Preparation of 2-methyl-6-nitro-2-(1-phenyl-1H-tetrazol-5-ylthiomethyl)-2,3-dihydroimidazo[2,1-b]oxazole

5 Sodium hydride (220 mg, 5.5 mmol) was added to a mixture of 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(1-phenyl-1H-tetrazol-5-ylthio)propane-2-ol prepared in Example 50 (2.1 g, 5.3 mmol) and 1,4-dioxane (40 ml), and the resulting mixture was stirred
10 under reflux for 24 hours. The reaction mixture was allowed to return to room temperature, and concentrated under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with ethyl acetate twice. The organic phases were combined,
15 washed with water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to
20 afford 2-methyl-6-nitro-2-(1-phenyl-1H-tetrazol-5-ylthiomethyl)-2,3-dihydroimidazo[2,1-b]oxazole (500 mg, yield 26%) as a light brown powder.
Melting point 140-147°C

Example 52

25 Preparation of tert-butyl(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino) acetate
Glycine tert-butyl ester monohydrochloride
(0.52 g, 2.27 mmol) in methylene chloride (5 ml) and

N,N-diisopropylethylamine (1.05 ml, 4.53 mmol) were added to a triphosgene (0.30 g, 0.76 mmol) in methylene chloride (10 ml) with cooling on ice-bath followed by stirring at room temperature for 2 hours. Insoluble matters were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was added to a solution of 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 33 (0.30 g, 1.51 mmol) in DMF (3 ml) with cooling on ice-bath. Then cuprous chloride (75 mg, 0.76 mmol) was added to the resulting mixture followed by stirring at room temperature for 22 hours. Water was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/2) to afford tert-butyl(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino)acetate (40 mg, yield 7%) as a white solid. Melting point 104-106°C

Example 53

Preparation of 6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl (4-morpholinophenyl)carbamate

1,1'-Carbonyldiimidazole (0.44 g, 2.69 mmol) was added to a solution of 4-morpholinoaniline (0.40 g, 2.24 mmol) in THF (4 ml) followed by stirring for 2

hours with cooling on ice-bath. The reaction mixture was filtered and washed with diethyl ether. The filtrate was added to a solution of 2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (0.30 g, 1.62 mmol) in DMF (3 ml) with cooling on ice-bath. Then, cuprous chloride (75 mg, 0.76 mmol) was added to the resulting mixture followed by stirring at room temperature for 2 hours. Water was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/acetone = 9/1), and washed with methylene chloride-ethyl acetate to afford 6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl (4-morpholinophenyl)carbamate (34 mg, yield 5%) as a white solid.

¹H-NMR (DMSO-d₆) δppm:

2.93 - 3.09 (4H, m), 3.64 - 3.80 (4H, m), 4.13 (1H, dd, J = 6.8 Hz, 10.9 Hz), 4.34 - 4.55 (3H, m), 5.55 - 5.73 (1H, m), 6.77 - 6.95 (2H, m), 7.18 - 7.41 (2H, m), 8.15 (1H, s), 9.52 (1H, br).

Example 54

Preparation of 2-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl 4-chlorophenylcarbamate

4-Chlorophenylisocyanate (169 ml, 1.1 mmol) and cuprous chloride (50 mg, 0.5 mmol) was added to a

solution of 2-hydroxyethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 31 (0.2 g, 1.0 mmol) in DMF (5 ml) with cooling on ice-bath followed by stirring at room temperature for 4 hours. The mixture was cooled on ice-bath and added 10% hydrochloric acid. The resulting mixture was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-isopropyl ether to afford 2-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl 4-chlorophenylcarbamate (0.16 g, yield 45%) as a white solid.

^1H -NMR (DMSO- d_6) δ ppm:
2.16 - 2.38 (2H, m), 4.08 (1H, dd, $J = 7.4$ Hz, 10.6 Hz), 4.16 - 4.36 (2H, m), 4.47 (1H, dd, $J = 7.4$ Hz, 10, 6 Hz), 5.44 - 5.55 (1H, m), 7.30 - 7.36 (2H, m), 7.46 - 7.52 (2H, m), 8.14 (1H, s), 9.83 (1H, br).

Using phenylisocyanate and 2-hydroxyethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole, 2-ethyl-2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole or 2-hydroxymethyl-2-isopropyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole gave compounds of Examples 55 to 57 in the same manner as in Example 54. In addition, using 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole and 3-

fluorophenylisocyanate or 4-tert-butoxycarbonylphenylisocyanate gave compounds of Examples 58 and 59 in the same manner as in Example 54.

Example 55

5 2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl phenylcarbamate

Yellow solid, yield 17%

¹H-NMR (DMSO-d₆) δppm:

1.63 (3H, s), 2.30 (2H, t, J = 6.9 Hz), 4.13 (1H, d, J
10 = 10.9 Hz), 4.21 - 4.32 (3H, m), 6.96 - 7.02 (1H, m),
7.24 - 7.27 (2H, m), 7.43 - 7.46 (2H, m), 8.12 (1H, s),
9.60 (1H, br).

Example 56

2-Ethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
15 ylmethyl phenylcarbamate

White solid, yield 60%

¹H-NMR (DMSO-d₆) δppm:

0.93 (3H, t, J = 7.4 Hz), 1.89 - 2.11 (2H, m), 4.19 -
4.29 (2H, m), 4.39 - 4.50 (2H, m), 6.99 (1H, t, J = 7.2
20 Hz), 7.23 - 7.29 (2H, m), 7.34 - 7.55 (2H, m), 8.14
(1H, s), 9.70 (1H, br).

Example 57

2-Isopropyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
ylmethyl phenylcarbamate

25 White solid, yield 73%

¹H-NMR (DMSO-d₆) δppm:

0.97 (6H, dd, J = 2.7 Hz, 6.9 Hz), 2.25 - 2.39 (1H, m),
4.20 (1H, d, J = 11.4 Hz), 4.30 (1H, d, J = 11.4 Hz),

4.48 (2H, s), 6.99 (1H, t, $J = 7.1$ Hz), 7.23 - 7.29 (2H, m), 7.32 - 7.52 (2H, m), 8.13 (1H, s), 9.67 (1H, br).

Example 58

- 5 2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 3-fluorophenylcarbamate

White solid, yield 71%

Melting point 168-169°C

Example 59

- 10 Tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino) benzoate

White solid, yield 32%

Melting point 177-178°C

Example 60

- 15 Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino)benzoic acid

Trifluoroacetic acid (1 ml) was added to a suspension of tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

- 20 ylmethoxycarbonylamino)benzoate prepared in Example 59 (185 ml, 0.44 mmol) in methylene chloride (10 ml) with cooling on ice-bath followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate. The solution was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was washed with ethyl acetate to afford 4-(2-methyl-6-

nitro-2,3-dihydromidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino)benzoic acid (50 mg, yield 31%) as a white solid.

Melting point 248°C (decomposition)

5 Example 61

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-chlorophenylcarbamate

2-Methyloxiran-2-ylmethyl 4-chlorophenylcarbamate (1.1 g, 4.4 mmol) and 2,4-dinitro-1H-imidazole (0.35 g, 2.2 mmol) were suspended in ethanol (1 ml), and the resulting mixture was stirred at room temperature for 24 hours. Then, sodium acetate (0.36 g, 4.4 mmol) and ethanol (2 ml) were added to the mixture followed by stirring under reflux for 6 hours. The reaction mixture was concentrated under reduced pressure. The residue was added water, and the resulting mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was crystallized from methylene chloride-diethyl ether to afford 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-chlorophenylcarbamate (0.17 g, yield 22%) as a light yellow solid.

Melting point 179-181°C

25 Example 62

Preparation of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-methylcarbamate

2-Methyloxiran-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate (1.7 g, 6.6 mmol) and 2-chloro-4-nitro-1H-imidazole (0.98 g, 6.6 mmol) were suspended in ethanol (10 ml) added sodium acetate (0.85 g, 10 mmol) followed by stirring under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure. A saturated aqueous sodium hydrogencarbonate was added to the residue, and the resulting mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-methylcarbamate (2.7 g, quantitative) as a light yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.15 (3H, br), 3.28 (3H, s), 3.78 - 4.28 (4H, m), 7.11 - 7.24 (2H, m), 7.30 - 7.41 (2H, m), 7.90 (1H, br).

Example 63

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate

Sodium hydride (0.32 g, 7.9 mmol) was added to a solution of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-methylcarbamate prepared in Example 62 (2.7 g, 6.6 mmol) in 1,4-dioxane (30 ml) with cooling on ice-bath

followed by stirring under reflux for 12 hours. The reaction mixture was concentrated under reduced pressure. The residue was cooled on ice-bath and added water, and the resulting solution was extracted with
5 methylene chloride. The extract was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) and crystallized from methylene chloride-ethanol to afford 2-methyl-6-
10 nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate (0.88 g, yield 36%) as a white solid.

Melting point 146-148°C

Example 64

15 Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-chlorophenylcarbamate

A THF solution (15 ml) of 4-chlorophenylisocyanate (1.3 g, 85 mmol) and triethylamine (0.1 ml) were added to a suspension of
20 (R)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (1.5 g, 6.5 mmol) in THF (30 ml) followed by stirring at room temperature for 19 hours. Insoluble matters were removed by filtration, and the filtrate was concentrated under
25 reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-

chlorophenylcarbamate (2.1 g, yield 83%) as a white solid.

¹H-NMR (DMSO-d₆) δppm:

1.15 (3H, s), 3.99 (2H, s), 4.07 (2H, s), 7.29 - 7.39
5 (2H, m), 7.45 - 7.58 (2H, m), 8.33 (1H, s), 9.86 (1H, br).

Using various kinds of corresponding phenylisocyanates gave compounds of Examples 65 to 69 in the same manner as in Example 64. In addition,
10 using benzylisocyanate or methylisocyanate gave compounds of Examples 70 and 71 in the same manner as in Example 64.

Example 65

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
15 methylpropyl 3-chlorophenylcarbamate
Yield 41%

¹H-NMR (DMSO-d₆) δppm:

1.15 (3H, s), 4.00 (2H, s), 4.13 (2H, s), 5.41 (1H, s),
7.04 - 7.09 (1H, m), 7.29 - 7.41 (2H, m), 7.55 - 7.66
20 (1H, m), 8.33 (1H, s), 9.93 (1H, br).

Example 66

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-bromophenylcarbamate
Yield 62%

25 ¹H-NMR (DMSO-d₆) δppm:

1.15 (3H, s), 3.99 (2H, s), 4.13 (2H, s), 5.40 (1H, s),
7.34 - 7.53 (4H, m), 8.33 (1H, s), 9.86 (1H, br).

Example 67

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-trifluoromethylphenylcarbamate

Yield 83%

¹H-NMR (DMSO-d₆) δppm:

5 1.16 (3H, s), 4.02 (2H, s), 4.14 (2H, s), 5.42 (1H, s),
7.58 - 7.74 (4H, m), 8.34 (1H, s), 10.14 (1H, br).

Example 68

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-trifluoromethoxyphenylcarbamate

10 Yield 58%

¹H-NMR (DMSO-d₆) δppm:

1.15 (3H, s), 3.99 (2H, s), 4.13 (2H, s), 5.41 (1H, s),
7.31 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz),
8.33 (1H, s), 9.92 (1H, br).

15 Example 69

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-fluorophenylcarbamate

Yield 95%

¹H-NMR (DMSO-d₆) δppm:

20 1.15 (3H, s), 3.98 (2H, s), 4.12 (2H, s), 5.39 (1H, s),
7.10 - 7.17 (2H, m), 7.45 - 7.51 (2H, m), 8.33 (1H, s),
9.73 (1H, br).

Example 70

25 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl benzylcarbamate

Yield 72%

¹H-NMR (CDCl₃) δppm:

1.20 (3H, s), 3.61 (1H, br), 3.97 - 4.04 (3H, m), 4.23

(1H, d, $J = 12.0$ Hz), 4.70 - 4.89 (1H, m), 7.13 - 7.39 (5H, m), 8.01 (1H, s).

Example 71

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl methylcarbamate

Yield 73%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.21 (3H, s), 2.80 (3H, d, $J = 4.8$ Hz), 3.57 (1H, br), 3.98 - 4.16 (3H, m), 4.24 (1H, d, $J = 12.3$ Hz), 4.72 - 4.91 (1H, m), 8.03 (1H, s).

Example 72

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (2.16 g, 9.18 mmol), N,N-diisopropylethylamine (2.67 ml, 15.30 mmol) and 4-dimethylaminopyridine (0.19 g, 1.53 mmol) were added to a suspension of N-methyl-N-(4-trifluoromethoxybenzyl)carbamoylechloride (2.05 g, 7.65 mmol) in toluene (40 ml) followed by stirring at 100°C for 3.5 hours. The reaction mixture was diluted with ethyl acetate, and the solution washed with 10% hydrochloric acid, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-

methylpropyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate (2.74 g, yield 77%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

5 1.25 (3H, s), 2.83 (3H, s), 3.87 - 4.17 (4H, m), 4.44 (2H, s), 7.18 - 7.25 (4H, m), 8.05 (1H, s).

Example 73

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate

Sodium hydride (0.28 g, 7.04 mmol) was added to a solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate prepared in Example 72
15 (2.74 g, 5.87 mmol) in DMF (20 ml) followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the precipitates were filtered off, washed with water and then recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate (1.40 g, yield 55%) as
20 a white solid.

Melting point 123-124°C

Example 74

25 Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-cyclohexylcarbamate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl-

propyl)-4-nitroimidazole prepared in Example 10 (0.95 g, 4.03 mmol), N, N-diisopropylethylamine (1.45 ml, 8.06 mmol) and 4-dimethylaminopyridine (0.10 g, 0.81 mmol) were added to a suspension of N-(4-chlorophenyl)-
 5 N-cyclohexylcarbamoylchloride (1.56 g, 6.05 mmol) in toluene (10 ml) followed by stirring at 100°C for 3 hours. The reaction mixture was diluted with ethyl acetate, and the solution was washed with 10% hydrochloric acid, dried over magnesium sulfate and
 10 then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl-N-(4-chlorophenyl)-N-cyclohexylcarbamate
 15 (0.75 g, yield 40%) as a white amorphous form.

¹H-NMR (CDCl₃) δppm:

0.78 - 1.22 (6H, m), 1.24 - 1.48 (2H, m), 1.54 - 1.67 (1H, m), 1.70 - 1.93 (4H, m), 2.87 - 3.13 (1H, m), 3.72 - 3.98 (3H, m), 4.00 - 4.24 (2H, m), 7.00 - 7.06 (2H,
 20 m), 7.35 - 7.41 (2H, m), 7.80 (1H, br).

Example 75

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-cyclohexylcarbamate

25 Sodium hydride (76 mg, 1.91 mmol) was added to a solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-cyclohexylcarbamate prepared in Example 74 (0.75 g,

1.59 mmol) in DMF (7 ml) followed by stirring for 0.5 hours with cooling on ice-bath. To the reaction mixture, ice-water was added, and the resulting mixture was extracted with ethyl acetate. The extract was
5 washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-cyclohexylcarbamate (0.53
10 g, yield 77%) as a white solid.
Melting point 175-177°C

Example 76

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoro-
15 methoxyphenyl)carbamate

N-Methyl-N-(4-trifluoromethoxyphenyl)-carbamoyl chloride (1.33 g, 5.23 mmol), N,N-diisopropylethylamine (1.2 ml, 6.97 mmol) and 4-dimethylaminopyridine (85 mg, 0.70 mmol) were added to
20 a suspension of (R)-2-chloro-1-(2,3-dihydroxy-2-methyl)propyl-4-nitroimidazole prepared in Example 10 (0.82 g, 3.48 mmol) in toluene (10 ml) followed by stirring at 100°C for 5 hours. The reaction mixture was diluted with ethyl acetate, and the solution was washed
25 with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford (R)-3-(2-chloro-

4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoromethoxyphenyl)carbamate (1.04 g, yield 65%) as a light yellow amorphous form.

¹H-NMR (DMSO-d₆) δppm:

5 1.02 (3H, s), 3.26 (3H, s), 3.80 - 4.00 (4H, m), 5.39 (1H, s), 7.37 - 7.40 (2H, m), 7.47 - 7.52 (2H, m), 8.25 (1H, s).

Example 77

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-methyl-N-(4-trifluoromethoxyphenyl)carbamate

Sodium hydride (0.48 g, 11.9 mmol) was added to a solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoromethoxyphenyl)carbamate prepared in Example 76 (4.50 g, 9.94 mmol) in DMF (13.5 ml) with cooling on ice-bath followed by stirring at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, and the precipitates were filtered off. The precipitates were recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-methyl-N-(4-trifluoromethoxyphenyl)carbamate (2.95 g, yield 71%) as a light yellow solid.

25 Melting point 144-145°C

Optical purity 99.8% e.e.

$[\alpha]_D^{24} = 7.68^\circ$ (concentration: 0.938, CHCl₃)

Using corresponding starting materials gave

compounds of Examples 78 and 79 in the same manner as in Example 77.

Example 78

(R)-2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methylcarbamate

Yield 26%, melting point 175-178°C

Example 79

(R)-2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl diethylcarbamate

Yield 27%, melting point 196-197°C

Example 80

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate

Iodomethane (0.71 ml, 11.4 mmol) and potassium hydroxide (0.64 g, 11.4 mmol) were added to a solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-chlorophenylcarbamate prepared in Example 64 (1.5 g, 3.8 mmol) in DMSO (40 ml) followed by stirring at room temperature for 4 hours. The mixture was cooled on ice-bath and added 10% hydrochloric acid. The resulting mixture was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate (0.67 g, 60%) as a white solid.

Melting point 131-133°C

5 Optical purity 99.8% e.e.

$[\alpha]_D^{26} = 22.86^\circ$ (concentration: 1.028, CHCl_3)

Example 81

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl bis(4-

10 chlorophenyl)carbamate

Pyridine (0.37 ml, 4.5 mmol) and triphosgene (0.16 g, 0.5 mmol) were added to a suspension of (R)-2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 37 (0.30 g, 1.5 mmol) in
15 methylene chloride (15 ml) with cooling on ice-bath followed by stirring at room temperature for 2.5 hours. To the reaction mixture, bis(4-chlorophenyl)amine (0.39 g, 1.6 mmol) was added, and the resulting mixture was stirred at room temperature for 20 hours. The reaction
20 mixture was cooled on ice-bath and added 10% hydrochloric acid. The resulting mixture was extracted with methylene chloride, and the extract was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silicagel column
25 chromatography (methylene chloride/ethyl acetate = 19/1) and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl bis(4-chlorophenyl)carbamate (82 mg, yield

12%) as a white solid.

Melting point 200-201°C

Example 82

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
5 b]oxazol-2-ylmethyl piperidine-1-carboxylate

Pyridine (0.37 ml, 4.5 mmol) and triphosgene
(0.18 g, 0.6 mmol) were added to a suspension of 2-
hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazole prepared in Example 33 (0.3 g, 1.5 mmol) in
10 methylene chloride (15 ml) with cooling on ice-bath
followed by stirring at room temperature for 2 hours.
The reaction mixture was cooled on ice-bath and added
piperidine (0.16 ml, 1.7 mmol). The resulting mixture
was stirred at room temperature for 3 hours. The
15 reaction mixture was cooled on ice-bath and added 10%
hydrochloric acid, and the insoluble matters were
removed by filtration. The filtrate was extracted with
methylene chloride, and the organic phase was dried
over magnesium sulfate and then concentrated under
20 reduced pressure. The residue was purified by silica
gel column chromatography (n-hexane/ethyl acetate =
3/2) and recrystallized from methylene chloride-
diisopropyl ether to afford 2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl piperidine-1-
25 carboxylate (65 mg, yield 14%) as a white solid.

Melting point 152-154°C

Example 83

Preparation of 3-(2-chloro-4-nitroimidazol-1-yl)-2-

hydroxy-2-methylpropyl 4-(4-trifluoromethoxyphenyl)-
piperazine-1-carboxylate

4-(4-Trifluoromethoxyphenyl)piperazine-1-
carbonylchloride (0.26 g, 0.85 mmol), N, N-
5 diisopropylethylamine (0.30 ml, 1.7 mmol) and 4-
dimethylaminopyridine (21 mg, 0.17 mmol) were added to
a suspension of 2-chloro-1-(2,3-dihydroxy-2-
methylpropyl)-4-nitroimidazol prepared in Example 3
(0.30 g, 1.3 mmol) in toluene (5 ml) followed by
10 stirring at 100°C for 2.5 hours. The mixture was
diluted with ethyl acetate, washed with water, dried
over magnesium sulfate and then concentrated under
reduced pressure. The residue was purified by silica
gel column chromatography (methylene chloride/ethyl
15 acetate = 9/1) to afford 3-(2-chloro-4-nitroimidazol-1-
yl)-2-hydroxy-2-methylpropyl 4-(4-
trifluoromethoxyphenyl)piperazine-1-carboxylate (0.24
g, yield 55%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

20 1.26 (3H, s), 3.02 - 3.17 (4H, m), 3.39 - 3.72 (4H, m),
3.91 (1H, s), 3.99 - 4.18 (3H, m), 4.34 (1H, d, J =
12.3 Hz), 6.85 - 6.98 (2H, m), 7.09 - 7.22 (2H, m),
8.05 (1H, s).

Example 84

25 Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazol-2-ylmethyl 4-(4-trifluoromethoxyphenyl)-
piperazine-1-carboxylate

Sodium hydride (23 mg, 0.56 mmol) was added

to a solution of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethoxyphenyl)-piperazine-1-carboxylate prepared in Example 83 (0.24 g, 0.47 mmol) in DMF (2 ml) followed by stirring at 0°C
5 for 1 hour. Ice-water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by
10 silica gel column chromatography (ethyl acetate) and then washed with diisopropyl ether to afford 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate (0.13 g, yield 58%) as a white solid.
15 Melting point 138-140°C

Example 85

Preparation of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate
20 2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 3 (0.13 g, 0.57 mmol), N,N-diisopropylethylamine (0.13 ml, 0.76 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were added to a suspension of 4-(4-trifluoromethylphenyl)-
25 1,2,3,6-tetrahydropyridine-1-carbonylchloride (0.10 g, 0.38 mmol) in toluene (3 ml) followed by stirring at 100°C for 2.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water, dried over

magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.11 g, yield 59%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.26 (3H, s), 2.43 - 2.50 (2H, m), 3.50 - 3.78 (2H, m),
 10 3.93 - 4.24 (5H, m), 7.46 (1H, d, $J = 8.3$ Hz), 7.60
 (1H, d, $J = 8.3$ Hz), 8.05 (1H, s).

Example 86

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate

Sodium hydride (11 mg, 0.28 mmol) was added to a solution of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate prepared in
 20 Example 85 (0.11 g, 0.23 mmol) in DMF (1 ml) followed by stirring for 1 hour with cooling on ice-bath. Ice-water was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and
 25 then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 4/1) and then washed with diisopropyl ether to afford 2-methyl-6-

nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.04 g, yield 39%) as a white solid.

Melting point 113-115°C

5 Example 87

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-tert-butoxycarbonylpiperazine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl-
10 propyl)-4-nitroimidazole prepared in Example 10 (4.43 g, 18.79 mmol), N,N-diisopropylethylamine (4.68 ml, 26.84 mmol) and 4-dimethylaminopyridine (0.33 g, 2.68 mmol) were added to a suspension of tert-butyl 4-chlorocarbonylpiperazine-1-carboxylate (3.34 g, 13.42
15 mmol) in toluene (70 ml), and the resulting mixture was stirred at 100°C for 4.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by
20 silica gel column chromatography (n-hexane/methylene chloride/ethyl acetate = 45/45/10) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-tert-butoxycarbonylpiperazine-1-carboxylate (4.12 g, yield 69%) as a colorless oil.

25 ¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 1.47 (9H, s), 3.33 - 3.50 (8H, m), 3.91 (1H, s), 3.99 - 4.16 (3H, m), 4.30 (1H, d, J = 12.1 Hz), 8.04 (1H, s).

Using 4-(4-trifluoromethoxybenzyloxy-carbonyl)piperazine-1-carbonylchloride or 4-[3-(4-trifluoromethylphenyl)-2-propenyloxycarbonyl]-piperazine-1-carbonylchloride gave compounds of

5 Examples 88 and 89 in the same manner as in Example 87.

Example 88

(R)-2-Chloro-1-{3-[4-(4-trifluoromethoxybenzyloxy-carbonyl)piperazin-1-ylcarbonyloxy]-2-hydroxy-2-methyl-propyl}-4-nitroimidazole

10 Yield 81%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 3.28 - 3.61 (8H, m), 3.89 (1H, s), 4.00 - 4.20 (3H, m), 4.31 (1H, d, J = 12.5 Hz), 5.14 (2H, s), 7.22 (2H, d, J = 8.7 Hz), 7.39 (2H, d, J = 8.7 Hz),

15 8.04 (1H, s).

Example 89

(R)-2-Chloro-1-{3-[4-[3-(4-trifluoromethylphenyl)-2-propenylcarbonyl]piperazin-1-ylcarbonyloxy]-2-hydroxy-2-methylpropyl}-4-nitroimidazole

20 Yield 95%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 3.33 - 3.61 (8H, m), 3.90 (1H, s), 3.99 - 4.17 (3H, m), 4.31 (1H, d, J = 12.1 Hz), 4.79 (2H, d, J = 6.1 Hz), 6.39 (1H, dt, J = 6.1 Hz, 15.9 Hz), 6.67

25 (1H, d, J = 15.9 Hz), 7.39 (2H, d, J = 8.3 Hz), 7.49 (2H, d, J = 8.3 Hz), 8.04 (1H, s).

Example 90

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-

hydroxy-2-methylpropyl 4-(4-chlorobenzyl)piperazine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl)propyl-4-nitroimidazole prepared in Example 10
 5 (2.28 g, 9.66 mmol), N,N-diisopropylethylamine (2.81 ml, 16.10 mmol) and 4-dimethylaminopyridine (0.20 g, 1.61 mmol) were added to a suspension of 4-(4-chlorobenzyl)piperazine-1-carbonylchloride (2.20 g, 8.05 mmol) in toluene (30 ml) followed by stirring 100°C
 10 for 3 hours. The reaction mixture was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1)
 15 to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-chlorobenzyl)piperazine-1-carboxylate (1.82 g, yield 48%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 2.17 - 2.50 (4H, m), 2.55 (1H, s), 3.26 -
 20 3.52 (6H, m), 3.98 - 4.20 (3H, m), 4.30 (1H, d, J = 12.4 Hz), 7.23 - 7.32 (4H, m), 8.05 (1H, s).

Using corresponding starting materials gave compounds of Examples 91 and 92 in the same manner as in Example 90.

25 Example 91

(R)-2-Chloro-1-{3-[4-(4-trifluoromethylbenzyl)-piperazin-1-ylcarbonyloxy]-2-hydroxy-2-methylpropyl}-4-nitroimidazole

Yield 31%

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 2.24 - 2.54 (4H, m), 3.24 - 3.50 (4H, m),
3.56 (2H, s), 3.97 - 4.20 (3H, m), 4.32 (1H, d, J =
5 12.4 Hz), 7.45 (2H, d, J = 8.0 Hz), 7.58 (2H, d, J =
8.0 Hz), 8.05 (1H, s).

Example 92

(R)-2-Chloro-1-{3-[4-(4-trifluoromethoxybenzyl)-
piperazin-1-ylcarbonyloxy]-2-hydroxy-2-methylpropyl}-4-
10 nitroimidazole

Yield 47%

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 2.22 - 2.54 (4H, m), 3.30 - 3.54 (4H, m),
3.50 (2H, s), 3.97 - 4.16 (3H, m), 4.32 (1H, d, J =
15 12.5 Hz), 7.15 - 7.18 (2H, m), 7.32 - 7.36 (2H, m),
8.05 (1H, s).

Example 93

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-
hydroxy-2-methylpropyl 4-(4-trifluoromethoxy-
20 phenyl)piperazine-1-carboxylate

4-(4-Trifluoromethoxyphenyl)piperazine-1-
carbonylchloride (1.25 g, 4.2 mmol), N, N-
diisopropylethylamine (0.96 ml, 5.6 mmol) and 4-
dimethylaminopyridine (67 mg, 0.56 mmol) were added to
25 a suspension of (R)-2-chloro-1-(2,3-dihydroxy-2-
methylpropyl)-4-nitroimidazole prepared in Example 10
(0.65 g, 2.8 mmol) in toluene (13 ml) followed by
stirring at 100°C for 8.5 hours. The reaction mixture

was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene

5 chloride/ethyl acetate = 19/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate (1.29 g, yield 92%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

10 1.26 (3H, s), 3.02 - 3.17 (4H, m), 3.39 - 3.72 (4H, m), 3.91 (1H, s), 3.99 - 4.18 (3H, m), 4.34 (1H, d, J = 12.3 Hz), 6.85 - 6.98 (2H, m), 7.09 - 7.22 (2H, m), 8.05 (1H, s).

Using corresponding starting materials gave
15 compounds of Examples 94 to 102 in the same manner as in Example 93.

Example 94

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)piperazine-1-
20 carboxylate

Yield 48%

¹H-NMR (CDCl₃) δppm:

1.26 (3H, s), 3.13 - 3.35 (4H, m), 3.48 - 3.72 (4H, m), 3.94 (1H, s), 4.00 - 4.18 (3H, m), 4.33 (1H, d, J =
25 12.3 Hz), 6.93 (2H, d, J = 8.6 Hz), 7.50 (2H, d, J = 8.6 Hz), 8.05 (1H, s).

Example 95

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-

methylpropyl 4-(4-methoxyphenyl)piperazine-1-carboxylate

Yield 54%

¹H-NMR (CDCl₃) δppm:

- 5 1.24 (3H, s), 2.93 - 3.09 (4H, m), 3.52 - 3.63 (4H, m),
3.77 (3H, s), 3.96 (1H, s), 4.00 - 4.19 (3H, m), 4.32
(1H, d, J = 12.3 Hz), 6.82 - 6.92 (4H, m), 8.05 (1H,
s).

Example 96

- 10 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-(4-chlorophenyl)piperazine-1-carboxylate
Yield 81%

¹H-NMR (CDCl₃) δppm:

- 1.25 (3H, s), 3.00 - 3.13 (4H, m), 3.52 - 3.65 (4H, m),
15 3.93 (1H, s), 4.00 - 4.17 (3H, m), 4.33 (1H, d, J =
12.5 Hz), 6.82 - 6.86 (2H, m), 7.20 - 7.25 (2H, m),
8.05 (1H, s).

Example 97

- (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
20 methylpropyl 4-(3-chlorophenyl)piperazine-1-carboxylate
Yield 87%

¹H-NMR (CDCl₃) δppm:

- 1.25 (3H, s), 3.04 - 3.22 (4H, m), 3.43 - 3.70 (4H, m),
3.89 (1H, s), 4.00 - 4.17 (3H, m), 4.33 (1H, d, J =
25 12.3 Hz), 6.78 (1H, ddd, J = 1.6 Hz, 2.4 Hz, 8.4 Hz),
6.85 - 6.88 (2H, m), 7.19 (1H, t, J = 8.4 Hz), 8.05
(1H, s).

Example 98

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(3,4-dichlorophenyl)piperazine-1-carboxylate

Yield 47%

5 ¹H-NMR (DMSO-d₆) δppm:

1.12 (3H, s), 3.15 - 3.26 (4H, m), 3.39 - 3.61 (4H, m),
3.88 (1H, d, J = 11.0 Hz), 3.93 (1H, d, J = 11.0 Hz),
4.07 (1H, d, J = 14.7 Hz), 4.15 (1H, d, J = 14.7 Hz),
6.96 (1H, dd, J = 2.9 Hz, 9.1 Hz), 7.16 (1H, d, J = 2.9
10 Hz), 7.42 (1H, d, J = 9.1 Hz), 8.34 (1H, s).

Example 99

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-fluorophenyl)piperazine-1-carboxylate

Yield 100%

15 ¹H-NMR (CDCl₃) δppm:

1.25 (3H, s), 2.96 - 3.09 (4H, m), 3.50 - 3.67 (4H, m),
3.98 (1H, s), 4.05 - 4.16 (3H, m), 4.33 (1H, d, J =
12.3 Hz), 6.85 - 7.02 (4H, m), 8.05 (1H, s).

Example 100

20 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(3-trifluoromethylphenyl)piperazine-1-carboxylate

Yield 83%

¹H-NMR (CDCl₃) δppm:

25 1.25 (3H, s), 3.11 - 3.26 (4H, m), 3.48 - 3.70 (4H,
m), 3.91 (1H, s), 4.00 - 4.24 (3H, m), 4.33 (1H, d, J =
12.3 Hz), 7.02 - 7.20 (3H, m), 7.38 (1H, t, J = 8.0
Hz), 8.05 (1H, s).

Example 101

(R)-2-Chloro-1-(3-diethylaminocarbonyloxy-2-hydroxy-2-methylpropyl)-4-nitroimidazole

Yield 37%

5 ¹H-NMR (CDCl₃) δppm:

1.11 (6H, t, J = 7.1 Hz), 1.20 (3H, s), 3, 16 (4H, q, J = 7.1 Hz), 3.76 (1H, br), 4.06 - 4.11 (3H, m), 4.26 (1H, d, J = 11.1 Hz), 8.05 (1H, s).

Example 102

10 2-Chloro-1-(3-morpholinocarbonyloxy-2-hydroxy-2-methylpropyl)-4-nitroimidazole

Yield 100%

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 3.35 - 3.52 (4H, m), 3.61 - 3.72 (4H, m),
15 3.99 - 4.16 (3H, m), 4.31 (1H, d, J = 12.3 Hz), 8.05 (1H, s).

Example 103

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-

20 trifluoromethylbenzylideneamino)piperazine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (2.75 g, 11.66 mmol), N,N-diisopropylethylamine (2.71 ml, 15.54 mmol) and 4-dimethylaminopyridine (0.19 g, 1.55 mmol) were added to a suspension of 4-(4-trifluoromethylbenzylideneamino)piperazine-1-carbonylchloride (2.48 g, 7.77 mmol) in toluene (40 ml)

followed by stirring at 100°C for 2.5 hours. The reaction mixture was diluted with ethyl acetate, washed with 10% hydrochloric acid, dried over magnesium sulfate and then concentrated under reduced pressure.

- 5 The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylbenzylideneamino)piperazine-1-carboxylate (4.03 g, quantitative) as a yellow oil.
- ¹H-NMR (CDCl₃) δppm:
- 1.25 (3H, s), 3.04 - 3.33 (4H, m), 3.48 - 3.76 (4H, m), 3.83 (1H, s), 4.00 - 4.17 (3H, m), 4.33 (1H, d, J = 12.3 Hz), 7.55 (1H, s), 7.59 (2H, d, J = 8.4 Hz), 7.69
- 15 (2H, d, J = 8.4 Hz), 8.04 (1H, s).

Example 104

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenoxy)piperidine-1-carboxylate

- 20 (R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (1.16 g, 4.68 mmol) and triethylamine (1.63 ml, 11.70 mmol) were added to a suspension of 4-(4-trifluoromethylphenoxy)piperidine-1-carbonylchloride (0.72 g, 2.34
- 25 mmol) in toluene (40 ml) followed by stirring at 100°C for 2.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and then concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenoxy)-piperidine-1-carboxylate (184 mg, yield 16%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 1.72 - 1.98 (4H, m), 3.33 - 3.67 (4H, m), 3.91 - 4.20 (3H, m), 4.24 - 4.39 (1H, m), 4.52 - 4.65 (1H, m), 6.96 (2H, d, J = 8.7 Hz), 7.55 (2H, d, J = 8, 7 Hz), 8.05 (1H, s).

Example 105

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl-amino)piperidine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (1.54 g, 7.01 mmol), N,N-diisopropylethylamine (1.63 ml, 9.34 mmol) and 4-dimethylaminopyridine (0.11 g, 0.93 mmol) were added to a suspension of 4-(4-trifluoromethylphenylamino)piperidine-1-carbonylchloride (1.43 g, 4.67 mmol) in toluene (30 ml) followed by stirring at 100°C for 2.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and then concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-

hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl-amino)piperidine-1-carboxylate (1.44 g, yield 61%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

5 1.25 (3H, s), 1.30 - 1.48 (2H, m), 1.98 - 2.13 (2H, m), 2.83 - 3.13 (2H, m), 3.37 - 3.61 (1H, m), 3.83 - 3.96 (2H, m), 3.96 - 4.22 (4H, m), 4.34 (1H, d, J = 11.8 Hz), 7.40 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 8.07 (1H, s).

10 Example 106

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl)-
15 propyl-4-nitroimidazole prepared in Example 10 (0.74 g, 3.11 mmol) and triethylamine (1.74 ml, 12.42 mmol) were added to a suspension of 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride (0.60 g, 2.07 mmol) in toluene (36 ml) followed by stirring at
20 100°C for 16 hours. The mixture was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1)
25 to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.32 g, yield 31%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

1.26 (3H, s), 2.43 - 2.50 (2H, m), 3.50 - 3.78 (2H, m),
3.93 - 4.24 (5H, m), 7.46 (2H, d, J = 8.3 Hz), 7.60
(2H, d, J = 8.3 Hz), 8.05 (1H, s).

5 Using corresponding starting materials gave
compounds of Examples 107 to 112 in the same manner as
in Example 106.

Example 107

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
10 methylpropyl 4-(4-chlorophenyl)-1,2,3,6-
tetrahydropyridine-1-carboxylate

Yield 94%

¹H-NMR (CDCl₃) δppm:

1.25 (3H, s), 2.41 - 2.59 (2H, m), 3.50 - 3.78 (2H, m),
15 3.93 - 4.22 (6H, m), 4.35 (1H, d, J = 12.3 Hz), 5.87 -
6.13 (1H, m), 7.26 - 7.37 (4H, m), 8.05 (1H, s).

Example 108

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-(4-trifluoromethoxyphenyl)-1,2,3,6-
20 tetrahydropyridine-1-carboxylate

Yield 92%

¹H-NMR (CDCl₃) δppm:

1.26 (3H, s), 2.46 - 2.59 (2H, m), 3.13 - 3.37 (1H, m),
3.50 - 3.74 (2H, m), 4.00 - 4.14 (6H, m), 4.36 (1H, d,
25 J = 12.4 Hz), 7.19 (2H, d, J = 8.0 Hz), 7.37 (2H, d, J
= 8.0 Hz), 8.05 (1H, s).

Example 109

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-

methylpropyl 4-(4-methoxyphenyl)-1,2,3,6-tetrahydro-
pyridine-1-carboxylate

Yield 63%

¹H-NMR (CDCl₃) δppm:

- 5 1.23 (3H, s), 2.43 - 2.61 (2H, m), 3.52 - 3.74 (2H, m),
3.82 (3H, s), 4.01 - 4.16 (5H, m), 4.34 (1H, d, J =
12.6 Hz), 5.83 - 6.00 (1H, m), 6.88 (2H, d, J = 8.8
Hz), 7.30 (2H, d, J = 8.8 Hz), 8.05 (1H, s).

Example 110

- 10 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-(3-trifluoromethylphenyl)-1,2,3,6-
tetrahydropyridine-1-carboxylate

Yield 54%

¹H-NMR (CDCl₃) δppm:

- 15 1.25 (3H, s), 2.46 - 2.70 (2H, m), 3.50 - 3.78 (2H, m),
4.00 - 4.32 (6H, m), 4.35 (1H, d, J = 12.6 Hz), 5.98 -
6.22 (1H, m), 7.39 - 7.67 (4H, m), 8.06 (1H, s).

Example 111

- 20 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-(4-bromophenyl)-1,2,3,6-
tetrahydropyridine-1-carboxylate

Yield 80%

¹H-NMR (CDCl₃) δppm:

- 25 1.25 (3H, s), 2.41 - 2.63 (2H, m), 3.50 - 3.76 (2H, m),
3.96 - 4.20 (6H, m), 4.35 (1H, d, J = 12.3 Hz), 5.87 -
6.13 (1H, m), 7.15 - 7.26 (2H, m), 7.43 - 7.48 (2H, m),
8.05 (1H, s).

Example 112

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate

Yield 57%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.25 (3H, s), 2.41 - 2.63 (2H, m), 3.50 - 3.76 (2H, m), 3.89 - 4.22 (6H, m), 4.35 (1H, d, $J = 12.6$ Hz), 5.83 - 6.04 (1H, m), 6.99 - 7.06 (2H, m), 7.29 - 7.35 (2H, m), 8.05 (1H, s).

10 Using 5-chloro-2,3-dihydroindole-1-carbonylchloride, 5-chloro-1,3-dihydroisoindol-2-carbonylchloride, 6-chloro-3,4-dihydro-1H-isoquinoline-2-carbonylchloride or 6-chloro-3,4-dihydro-2H-quinoline-1-carbonylchloride gave compounds of Examples
15 113 to 116 in the same manner as in Example 106.

Example 113

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 5-chloroindolinyl-1-carboxylate

Light yellow amorphous form, yield 50%

20 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.27 (3H, s), 3.14 (2H, t, $J = 8.5$ Hz), 3.42 (1H, br), 3.91 - 4.28 (5H, m), 4.37 (1H, d, $J = 11.8$ Hz), 7.04 - 7.24 (2H, m), 7.73 (1H, d, $J = 8.3$ Hz), 8.04 (1H, s).

Example 114

25 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 5-chloroisoindolinyl-2-carboxylate

Brown solid, yield 19%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.27 (3H, s), 3.93 (1H, d, $J = 7.8$ Hz), 4.04 - 4.24 (7H, m), 4.32 (1H, d, $J = 11.8$ Hz), 7.16 - 7.29 (3H, m), 8.07 (1H, s).

Example 115

- 5 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 6-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate

Light yellow oil, yield 63%

$^1\text{H-NMR}$ (CDCl_3) δppm :

- 10 1.24 (3H, s), 2.83 (2H, t, $J = 5.8$ Hz), 3.46 - 3.76 (2H, m), 3.90 (1H, d, $J = 5.3$ Hz), 4.01 - 4.15 (3H, m), 4.34 (1H, d, $J = 12.3$ Hz), 4.43 - 4.65 (2H, m), 6.93 - 7.09 (1H, m), 7.09 - 7.22 (2H, m), 8.04 (1H, s).

Example 116

- 15 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 6-chloro-3,4-dihydro-2H-quinoline-1-carboxylate

Light yellow oil, yield 70%

$^1\text{H-NMR}$ (CDCl_3) δppm :

- 20 1.26 (3H, s), 1.87 - 2.00 (2H, m), 2.76 (2H, t, $J = 6.5$ Hz), 3.27 (1H, br), 3.57 - 3.83 (2H, m), 3.98 - 4.17 (3H, m), 4.33 (1H, d, $J = 12.0$ Hz), 7.12 - 7.16 (2H, m), 7.41 - 7.61 (1H, br), 7.98 (1H, s).

Example 117

- 25 Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-tert-butoxycarbonylpiperazine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-

nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-tert-butoxycarbonylpiperazine-1-carboxylate prepared in Example 87 (4.12 g, 9.20 mmol) in DMF (30 ml), sodium hydride (0.44 g, 11.04 mmol) was added followed by
5 stirring for 1 hour with cooling on ice-bath. Ice-water was added to the reaction mixture, and the precipitates were filtered off, purified by silica gel column chromatography (ethyl acetate) and then washed with isopropanol to afford (R)-2-methyl-6-nitro-2,3-
10 dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-tert-butoxycarbonylpiperazine-1-carboxylate (2.24 g, yield 59%) as a white solid.
Melting point 211-212°C.

Example 118

15 Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-
20 trifluoromethoxyphenyl)piperazine-1-carboxylate prepared in Example 93 (1.29 g, 2.5 mmol) in DMF (13 ml), sodium hydride (0.12 g, 3 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice water was added, and the
25 precipitates were filtered off, washed with water and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate

(0.70 g, yield 59%) as a white solid.

Optical purity 99.6% e.e.

$[\alpha]_D^{25} = 0.99^\circ$ (concentration: 0.704, CHCl_3)

Melting point 168-169°C.

5 Example 119

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-chlorobenzyl)piperazine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-chlorobenzyl)piperazine-1-carboxylate prepared in Example 90 (1.82 g, 3.85 mmol) in DMF (10 ml), sodium hydride (0.31 g, 7.70 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the precipitates were filtered off and washed with isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-chlorobenzyl)piperazine-1-carboxylate (0.46 g, yield 28%) as a light yellow solid.

Melting point 161-163°C.

 Example 120

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylbenzylideneamino)piperazine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-

trifluoromethylbenzylideneamino)piperazine-1-carboxylate prepared in Example 103 (4.03 g, 7.77 mmol) in DMF (20 ml), sodium hydride (0.37 g, 9.32 mmol) was added followed by stirring for 1 hour with cooling on
5 ice-bath. To the reaction mixture, ice water was added, and the precipitates were filtered off, washed with water and recrystallized from acetonitrile-isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-
10 trifluoromethylbenzylideneamino)piperazine-1-carboxylate (2.60 g, yield 69%) as a white solid. Melting point 176-178°C.

Example 121

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-
15 trifluoromethylphenylamino)piperidine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenylamino)piperidine-1-carboxylate
20 prepared in Example 105 (1.44 g, 2.85 mmol) in DMF (10 ml), sodium hydride (0.14 g, 3.42 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The
25 organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) and

recrystallized from acetonitrile-isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenylamino)piperidine-1-carboxylate (0.42 g, yield 31%) as a white solid.

5 Melting point 137-140°C.

Example 122

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenoxy)piperidine-1-carboxylate

10 To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenoxy)piperidine-1-carboxylate prepared in Example 104 (0.18 g, 0.36 mmol) in DMF (2 ml), sodium hydride (19 mg, 0.47 mmol) was added
15 followed by stirring for 1.5 hours with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced
20 pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenoxy)piperidine-1-
25 carboxylate (0.08 g, yield 47%) as a white solid.
Melting point 165-166°C.

Example 123

Preparation of (R)-2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate prepared in Example 106 (0.32 g, 0.65 mmol) in DMF (3 ml), sodium hydride (31 mg, 0.78 mmol) was added followed by stirring for 1.5 hours with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.14 g, yield 49%) as a white solid. Optical purity 98.4% e.e.
 $[\alpha]_D^{26} = 2.50^\circ$ (c0.560, CHCl₃).
 Melting point 169-171°C.

Example 124

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 5-chloro-2,3-dihydroindole-1-carboxylate

To the solution of (R)-3-(2-chloro-4-

nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 5-chloro-2,3-dihydroindole-1-carboxylate prepared in Example 113 (0.60 g, 1.44 mmol) in DMF (6 ml), sodium hydride (70 mg, 1.73 mmol) was added followed by stirring 1 hour
5 with cooling on ice-bath. To the reaction mixture, ice-water was added, and the precipitates were filtered off, washed with water and recrystallized from acetonitrile-isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 5-chloro-2,3-dihydroindole-1-carboxylate (0.30 g, yield
10 55%) as a white solid.
Melting point 189-191°C.

Example 125

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 5-chloro-1,3-dihydroisoindol-2-carboxylate
15

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 5-chloro-1,3-dihydro-isoindol-2-carboxylate prepared in Example
20 114 (0.13 g, 0.31 mmol) in DMF (2 ml), sodium hydride (15 mg, 0.37 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was
25 washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to afford (R)-2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl 5-chloro-1,3-dihydroisoindole 2-carboxylate (7 mg, yield 6%) as a light yellow solid.

Melting point 182°C (decomposition).

5 Example 126

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 6-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 6-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate prepared in Example 115 (0.26 g, 0.61 mmol) in DMF (2 ml), sodium hydride (30 mg, 0.73 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate, concentrated under reduced pressure and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 6-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate (0.12 g, 49%) as a light yellow solid.

Melting point 180-182°C.

 Example 127

25 Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 6-chloro-3,4-dihydro-2H-quinoline-1-carboxylate

To the solution of (R)-3-(2-chloro-4-

nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 6-chloro-3,4-dihydro-2H-quinoline-1-carboxylate prepared in Example 116 (1.84 g, 4.29 mmol) in DMF (10 ml), sodium hydride (0.21 g, 5.15 mmol) was added followed by

5 stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue

10 was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) and recrystallized from acetonitrile-isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 6-chloro-3,4-dihydro-2H-quinoline-1-

15 carboxylate (0.68 g, yield 40%) as a white solid. Melting point 172-174°C.

Example 128

Preparation of 2-methyl-6-nitro-2-(4-trifluoromethoxyphenoxy-methyl)-2,3-dihydroimidazo[2,1-b]oxazole

20 4-Trifluoromethoxyphenol (198 mg, 1.11 mmol) was dissolved in DMF (5 ml). To the solution, sodium hydride (48 mg, 1.21 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the resulting solution, 2-chloro-1-(2-

25 methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (220 mg, 1.01 mmol) was added with cooling on ice-bath, and the solution was stirred for 15 minutes at 80°C. The reaction mixture was poured into ice-

water, and the mixture was extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride-diisopropyl ether to afford 2-methyl-6-nitro-2-(4-trifluoromethoxyphenoxyethyl)-2,3-dihydroimidazo[2,1-b]oxazole (170 mg, yield 47%) as a white powder.

Melting point 126.8-127.9°C

MS 358 (M-1)⁺

Example 129

Preparation of 2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethoxyphenoxy)piperidin]-1-ylphenol (244 mg, 0.69 mmol) was dissolved in DMF (10 ml). To the solution, sodium hydride (33 mg, 0.83 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (150 mg, 0.69 mmol) was added with cooling on ice-bath, and the solution was stirred at 80°C for 20 minutes. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed

with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced
5 pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride/ethyl acetate to afford 2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy-
10 methyl}-2,3-dihydroimidazo[2,1-b]oxazole (103 mg, yield 28%) as a white powder. Melting point 165.4-166.3°C.

Example 130

Preparation of 2-methyl-6-nitro-2-{4-[4-(4-trifluoro-
15 methylphenyl)piperazin-1-yl]phenoxy-2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethylphenyl)piperazin-1-yl]phenol (296 mg, 0.92 mmol) was dissolved in DMF (10 ml). To the solution, sodium hydride (44 mg, 1.1 mmol)
20 was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (200 mg, 0.92 mmol) was added with cooling on ice-bath, and the solution was stirred
25 for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene

chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by
5 silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride/ethyl acetate to afford 2-methyl-6-nitro-2-{4-[4-(4-trifluoromethylphenyl)piperazin-1-yl]phenoxyethyl}-
10 2,3-dihydroimidazo[2,1-b]oxazole (178 mg, yield 38%) as a white powder.
Melting point 230.7-233.1°C.

Example 131

Preparation of tert-butyl 4-[4-(2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate

Tert-butyl 4-(4-hydroxyphenyl)piperazine-1-carboxylate (2.01 g, 7.23 mmol) was dissolved in DMF (20 ml). To the solution, sodium hydride (320 mg, 8
20 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 70°C. To the solution, 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (1.5 g, 7.23 mmol) was added with cooling on ice-bath, and the solution was stirred for
25 further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The

solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel
5 column chromatography (methylene chloride/ethyl acetate = 20/1) and then crystallized from methylene chloride/ethyl acetate to afford tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate (1.5 g, yield
10 45%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.48 (9H, s), 1.77 (3H, s), 2.99 - 3.03 (4H, m), 3.55 -
3.59 (4H, m), 4.02 (1H, d, $J = 10.2$ Hz), 4.04 (1H, d, $J = 10.1$ Hz), 4.18 (1H, d, $J = 10.1$ Hz), 4.49 (1H, d, $J =$
15 10.2 Hz), 6.76 - 6.81 (2H, m), 6.84 - 6.89 (2H, m),
7.55 (1H, s).

Melting point 212.0-214.5°C

MS 459(M^+).

Example 132

20 Preparation of tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate

Tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (364 mg, 1.31 mmol) was dissolved in DMF
25 (10 ml). To the solution, sodium hydride (58 mg, 1.44 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole

prepared in Example 6 (300 mg, 1.38 mmol) was added with cooling on ice-bath followed by stirring for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred
5 vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated
10 under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and then crystallized from methylene chloride-diisopropyl ether to afford tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
15 b]oxazol-2-ylmethoxy)phenyl]piperidine-1-carboxylate (248 mg, yield 41%) as a white powder.
Melting point 207.8-209.1°C.

Example 133

Preparation of 3,4-dichlorobenzyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-
20 phenyl]piperazine-1-carboxylate

Tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine-1-carboxylate prepared in Example 131 (118
25 mg, 0.26 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated

under reduced pressure and added methylene chloride (2 ml) and triethylamine (2 ml). The solution was stirred at room temperature for 5 minutes and then concentrated under reduced pressure. The residue was dissolved in 5 DMF (15 ml) and the solution was added a solution of 3,4-dichlorobenzyl alcohol (136 mg, 0.77 mmol) and 1,1'-carbonyldiimidazole (125 mg, 0.77 mmol) in DMF (5 ml) stirred at room temperature for 3 hours followed by stirring at room temperature overnight. The reaction 10 mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by 15 silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 3,4-dichlorobenzyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)- 20 phenyl]piperazine-1-carboxylate (101 mg, yield 70%) as a light yellow powder.

¹H-NMR (CDCl₃) δppm:

1.77 (3H, s), 3.01 - 3.06 (4H, m), 3.62 - 3.67 (4H, m),
4.02 (1H, d, J = 10.2 Hz), 4.04 (1H, d, J = 10.2 Hz),
25 4.18 (1H, d, J = 10.2 Hz), 4.49 (1H, d, J = 10.2 Hz),
5.09 (2H, s), 6.76 - 6.81 (2H, m), 6.84 - 6.89 (2H, m),
7.18 - 7.22 (1H, m), 7.41 - 7.47 (2H, m), 7.55 (1H, s).

Example 134

Preparation of 2-methyl-6-nitro-2-{4-[4-(4-trifluoro-methylbenzyl)piperazin-1-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 131 (88 mg, 0.19 mmol) was dissolved in trifluoroacetic acid (5 ml), and the solution was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (2 ml) and triethylamine (2 ml). The solution was stirred at room temperature for 5 minutes and then concentrated under reduced pressure. The residue was dissolved in dichloroethane and added 4-trifluoromethylbenzaldehyde (40 μ l, 0.29 mmol) and sodium triacetoxyborohydride (82 mg, 0.38 mmol) with cooling on ice-bath followed by stirring at room temperature overnight. To the solution, a saturated sodium hydrogencarbonate solution and methylene chloride were added. The mixture was extracted with methylene chloride, and the organic phase was dried over magnesium sulfate and filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-ethyl acetate to afford 2-methyl-6-nitro-2-{4-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole (53 mg, yield 53%) as

a white powder.

Melting point 171.8-173.1°C.

Using tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
5 piperidine-1-carboxylate prepared in Example 132 gave the compound of Example 135 in the same manner as in Example 134.

Example 135

2-Methyl-6-nitro-2-{4-[1-(4-trifluoromethoxybenzyl)-
10 piperidin-4-yl]phenoxy)methyl}-2,3-dihydroimidazo[2,1-b]oxazole

Yield 45%, melting point 160.6-161.1°C.

Example 136

Preparation of (R)-2-methyl-6-nitro-2-(4-trifluoro-
15 methoxyphenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole
4-Trifluoromethoxyphenol (1.1 g, 6.17 mmol) was dissolved in DMF (20 ml). To the solution, sodium hydride (260 mg, 6.45 mmol) was added at room temperature, and the solution was stirred for 15
20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (1.22 g, 5.61 mmol) was added with cooling on ice-bath, and the solution was stirred for further 2 hours at 80°C. The reaction mixture was poured into
25 ice-water, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over

magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride-diisopropyl ether to afford (R)-2-methyl-6-nitro-2-(4-trifluoromethoxyphenoxy-methyl)-2,3-dihydroimidazo[2,1-b]oxazole (1.03 g, yield 51%) as a white powder.

Optical purity >99% e.e.

$[\alpha]_D^{28} = 7.67^\circ$ (concentration: 1.030, CHCl_3)

MS 359 (M^+)

Melting point 176.5–178.0°C.

Using corresponding starting materials gave compounds of Examples 137 to 139 in the same manner as in Example 136.

Example 137

(R)-2-Methyl-6-nitro-2-[4-(thiomorpholin-4-yl)phenoxy-methyl]-2,3-dihydroimidazo[2,1-b]oxazole

Yield 38%, melting point 227.5–229.0°C, MS 376 (M^+).

Example 138

(R)-2-Methyl-6-nitro-2-[4-(imidazol-1-yl)phenoxy-methyl]-2,3-dihydroimidazo[2,1-b]oxazole

Yield 44%, melting point 172–175°C.

Example 139

(R)-2-Methyl-6-nitro-2-[4-(1,2,4-triazol-1-yl)phenoxy-methyl]-2,3-dihydroimidazo[2,1-b]oxazole

Yield 53%, melting point 236.0–238.7°C.

Using ethyl 1-(4-hydroxyphenyl)piperidine-4-carboxylate gave the compound of Example 140 in the same manner as in Example 136.

Example 140

- 5 Ethyl (R)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethoxy)phenyl]piperidine-4-carboxylate

Yield 30%, melting point 208.2-211.5°C.

Example 141

- 10 Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethoxyphenoxy)piperidin-1-yl]phenol (17.4 g, 49.0 mmol) was dissolved in DMF (150
15 ml). To the solution, sodium hydride (2.15 g, 53.8 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (14.9 g, 68.6
20 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the mixture was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in
25 methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride/ethyl acetate to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-

- 5 trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole (14.3 g, yield 55%) as a light yellow powder.

MS 535(M+1)⁺

Optical purity 99.9% e.e.

- 10 $[\alpha]_D^{28} = -9.94^\circ$ (concentration: 1.006, CHCl₃)

Melting point 194.5-196°C

¹H-NMR (CDCl₃) δ ppm:

- 1.77 (3H, s), 1.87 - 2.00 (2H, m), 2.05 - 2.16 (2H, m),
2.95 - 3.05 (2H, m), 3.32 - 3.41 (2H, m), 4.02 (1H, d,
15 J = 10.2 Hz), 4.04 (1H, d, J = 10.2 Hz), 4.18 (1H, d, J = 10.2 Hz), 4.36 - 4.45 (1H, m), 4.49 (1H, d, J = 10.2 Hz), 6.74 - 6.81 (2H, m), 6.87 - 6.94 (4H, m), 7.11 - 7.16 (2H, m), 7.55 (1H, s).

Example 142

- 20 Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole

- 4-[4-(4-Trifluoromethoxyphenyl)piperazin-1-yl]phenol (1.7 g, 5.02 mmol) was dissolved in DMF (20
25 ml). To the solution, sodium hydride (221 mg, 5.53 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-

nitroimidazole prepared in Example 12 (1.2 g, 5.53 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then recrystallized from ethyl acetate to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole (1.02 g, yield 39%) as a light yellow powder.

MS 519(M⁺)

Optical purity >99% e.e.

$[\alpha]_D^{28} = -18.02^\circ$ (concentration: 1.160, CHCl₃)

Melting point 262.5-265°C.

Example 143

Preparation of tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate

Tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (1.07 g, 3.86 mmol) was dissolved in DMF (10 ml). To the solution, sodium hydride (185 mg, 4.63 mmol) was added at room temperature, and the solution

was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (923 mg, 4.24 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and then crystallized from ethyl acetate-diisopropyl ether to afford tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperidine-1-carboxylate (857 mg, yield 48%) as a white powder.

MS 458 (M⁺)

Optical purity >99% e.e.

$[\alpha]_D^{28} = -1.07^\circ$ (concentration: 1.028, CHCl₃)

Melting point 227.5-228.3°C (decomposition).

Using corresponding starting materials gave the compound of Example 144 in the same manner as in Example 143.

Example 144

Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-

1,2,3,6-tetrahydropyridine-1-carboxylate

Melting point 183.0-189.0°C (decomposition).

Example 145

Preparation of tert-butyl (R)-4-[4-(2-methyl-6-nitro-
5 2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoyl]-
piperazine-1-carboxylate

Tert-butyl 4-(4-hydroxybenzoyl)piperazine-1-
carboxylate (6.6 g, 21.5 mmol) was dissolved in DMF
(50 ml). To the solution, sodium hydride (991 mg,
10 24.8 mmol) was added at room temperature, and the
solution was stirred for 20 minutes at 80°C. To the
solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-
nitroimidazole prepared in Example 12 (5.16 mg,
23.7 mmol) was added with cooling on ice-bath, and the
15 solution was stirred for further 20 minutes at 80°C. To
the reaction mixture, ice-water was added, and the
solution was stirred vigorously. The precipitates were
filtered off, washed with water, dissolved in methylene
chloride. The organic phase was washed with a
20 saturated saline solution, dried over magnesium sulfate
and then filtered. The resulting filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (methylene
chloride/methanol = 100/1) and then crystallized from
25 methylene chloride-diisopropyl ether to afford tert-
butyl (R)-4-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-
ylmethoxy)benzoyl]piperazine-1-carboxylate (7.35 g,

yield 70%) as a white powder.

MS 488 (M+1)⁺

Melting point 222.5-224.0°C.

Example 146

- 5 Preparation of tert-butyl (R)-4-[2-chloro-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-phenyl]piperazine-1-carboxylate

Tert-butyl 4-(2-chloro-4-hydroxyphenyl)-piperazine-1-carboxylate (2.7 g, 8.63 mmol) was
10 dissolved in DMF (20 ml). To the solution, sodium hydride (397 mg, 9.92 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12
15 (2.1 g, 9.50 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in
20 methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene
25 chloride/methanol = 200/1) and then crystallized from methylene chloride-ethyl acetate to afford tert-butyl (R)-4-[2-chloro-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethoxy)phenyl]piperazine-1-carboxylate (2.34 g, yield 55%) as a white powder.

MS 493(M⁺)

Melting point 207.0-209.5°C.

5 Example 147

Preparation of tert-butyl (R)-4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate

Tert-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate (3.23 g, 11.6 mmol) was dissolved in DMF (40 ml). To the solution, sodium hydride (557 mg, 13.9 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (2.78 g, 12.8 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and then crystallized from methylene chloride-ethyl acetate to afford tert-butyl (R)-4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate
(1.4 g, yield 26%) as a white powder.

MS 459(M⁺)

Melting point 179.5-182.0°C.

5 Example 148

Preparation of tert-butyl (R)-4-[4-(2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine-1-carboxylate

 Tert-butyl 4-(4-hydroxyphenyl)piperazine-1-
10 carboxylate (13.5 g, 48.8 mmol) was dissolved in DMF
(100 ml). To the solution, sodium hydride (2.15 g,
53.7 mmol) was added at room temperature, and the
solution was stirred for 20 minutes at 70°C. To the
solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-
15 nitroimidazole prepared in Example 12 (10.6 g, 48.8
mmol) was added with cooling on ice-bath, and the
solution was stirred for further 20 minutes at 80°C. To
the reaction mixture, ice-water was added, and the
solution was stirred vigorously. The precipitates were
20 filtered off, washed with water and dissolved in
methylene chloride. The solution was washed with a
saturated saline solution, dried over magnesium sulfate
and then filtered. The resulting filtrate was
concentrated under reduced pressure. The residue was
25 purified by silica gel column chromatography (methylene
chloride/methanol = 100/1) and then crystallized from
methylene chloride-ethyl acetate to afford tert-butyl
(R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate
(9.9 g, yield 44%) as a white powder.

Optical purity >99.5% e.e.

$[\alpha]_D^{28} = -10.85^\circ$ (concentration: 1.014, CHCl_3)

5 MS 459 (M^+)

Melting point 230-232°C

^1H -NMR (CDCl_3) δ ppm:

1.48 (9H, s), 1.76 (3H, s), 2.99 - 3.03 (4H, m), 3.54 -
3.59 (4H, m), 4.02 (1H, d, $J = 10.2$ Hz), 4.04 (1H, d, J
10 = 10.1 Hz), 4.18 (1H, d, $J = 10.1$ Hz), 4.49 (1H, d, J =
10.2 Hz), 6.76 - 6.81 (2H, m), 6.85 - 6.89 (2H, m),
7.58 (1H, s).

Example 149

Preparation of (R)-[4-(2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine dihydrochloride

Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine-1-carboxylate prepared in Example 148 (300
20 mg, 0.65 mmol) was dissolved in trifluoroacetic acid
(5 ml) followed by stirring at room temperature for 3
hours. The reaction mixture was concentrated under
reduced pressure, and the residue was dissolved in
methanol. To the solution, a saturated hydrogen
25 chloride (5 ml) in ethyl acetate was added, and the
precipitates were filtered off and dried under reduced
pressure to afford (R)-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-

phenyl]piperazine dihydrochloride (279 mg, yield 99%)
as a light yellow powder.

MS 359(M⁺)

Melting point 212-220°C (decomposition)

5 ¹H-NMR (DMSO-d₆) δppm:

1.67 (3H, s), 3.22 - 3.31 (8H, m), 4.18 (1H, d, J =
10.9 Hz), 4.23 (2H, s), 4.37 (1H, d, J = 10.9 Hz), 6.85
(2H, d, J = 9.1 Hz), 7.00 (2H, d, J = 9.1 Hz), 8.16
(1H, s), 9.37 (3H, br).

10 Example 150

Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-
trifluoromethylbenzyl)piperazin-1-yl]phenoxymethyl}-
2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (R)-4-[4-(2-methyl-6-
15 nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-
phenyl]piperazine-1-carboxylate prepared in Example 148
(800 mg, 1.74 mmol) and trifluoroacetic acid (3 ml) was
stirred at room temperature for 7 hours. The reaction
mixture was concentrated under reduced pressure, and
20 the residue was dissolved in methylene chloride
(10 ml). To the solution, triethylamine (3 ml, 21.52
mmol) was added followed by stirring at room
temperature for 5 minutes. The mixture was
concentrated under reduced pressure, and the residue
25 was dissolved in methanol (10 ml). To the solution, 4-
trifluoromethylbenzaldehyde (910 mg, 5.23 mmol), sodium
cyanotrihydroborate (328 mg, 5.23 mmol) and acetic acid
(0.33 ml, 5.23 mmol) were added followed by stirring at

room temperature overnight. To the reaction mixture, a saturated sodium hydrogencarbonate solution and methylene chloride were added, and the solution was stirred and then extracted with methylene chloride.

- 5 The organic phase was dried over magnesium sulfate and filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole (667 mg, yield 74%) as a light yellow powder. Melting point 205.5-207°C.

Example 151

- 15 Preparation of ethyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate

- Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 148 (300 mg, 0.65 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and then added methylene chloride (5 ml), triethylamine (2 ml) and ethyl chloroformate (0.11 ml, 1.31 mmol) followed by stirring at room temperature for 1 hour. The reaction mixture was

poured into water and extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was
5 concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford ethyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate (182 mg,
10 yield 65%) as a white powder.

$[\alpha]_D^{28} = -9.86^\circ$ (concentration: 1.014, CHCl_3).

MS 431 (M^+)

Melting point 210.5-212.0°C.

15 Example 152

Preparation of 4-chlorobenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-phenyl]piperazine-1-carboxylate

Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
20 piperazine-1-carboxylate prepared in Example 148 (300 mg, 0.65 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 3
25 hours. The reaction mixture was concentrated under reduced pressure and then added methylene chloride (2 ml) and triethylamine (2 ml). After stirring at room temperature for 5 minutes, the solution was

concentrated under reduced pressure, and the residue was dissolved in DMF (15 ml). To the solution, a mixture of 4-chlorobenzyl alcohol (186 mg, 1.31 mmol), 1,1'-carbonyldiimidazole (212 mg, 1.31 mmol) in DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. The reaction mixture was poured into water, extracted from ethyl acetate, and the organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 4-chlorobenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate (313 mg, yield 91%) as a light yellow powder.

$[\alpha]_D^{28} = -10.84^\circ$ (concentration: 1.006, CHCl_3)

MS 527 (M^+)

Melting point 184.5-187.5°C.

Using corresponding starting materials gave the compound of Example 153 in the same manner as in Example 152.

Example 153

5-Chlorobenzofuran-2-ylmethyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-phenyl]piperazine-1-carboxylate

Yield 79%, melting point 195-197°C.

Using tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate prepared in Example 143, tert-
5 butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethoxy)phenyl]-1,2,3,6-tetrahydro-
pyridine-1-carboxylate prepared in Example 144, tert-
butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethoxy)benzoyl]piperazine-1-
10 carboxylate prepared in Example 145, or tert-butyl (R)-
4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-
2-ylmethoxy)phenyl]piperazine-1-carboxylate prepared in
Example 147 gave compounds of Examples 154 to 158 in
the same manner as in Example 152.

15 Example 154

4-Trifluoromethoxybenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate

Yield 54%, melting point 202.5-204°C.

20 Example 155

4-Trifluoromethoxybenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-1,2,3,6-tetrahydropyridine-1-carboxylate

Yield 67%, melting point 174.3-174.8°C.

25 Example 156

4-Trifluoromethoxybenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoyl]-piperazine-1-carboxylate

Yield 86%, melting point 168.5-172°C.

Example 157

Ethyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethoxy)benzoyl]piperazine-1-

5 carboxylate

Yield 85%, melting point 132-135°C.

Example 158

4-Trifluoromethoxybenzyl (R)-4-[3-(2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-

10 piperazine-1-carboxylate

Yield 50%, melting point 136.5-138°C.

Example 159

Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-
trifluoromethoxybenzyl)piperazin-1-yl]phenoxyethyl}-

15 2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine-1-carboxylate prepared in Example 148 (4.22
g, 9.60 mmol) was dissolved in methylene chloride (10
20 ml). To the solution, trifluoroacetic acid (30 ml) was
added followed by stirring at room temperature for 5
hours. The reaction mixture was concentrated under
reduced pressure and added methylene chloride (10 ml)
and triethylamine (10 ml). The solution was stirred at
25 room temperature for 5 minutes and then concentrated
under reduced pressure. The residue was dissolved in
dichloroethane. To the solution, 4-
trifluoromethoxybenzaldehyde (1.64 ml, 11.5 mmol) and

sodium triacetoxyborohydride (3.05 g, 14.4 mmol) were added with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, a saturated sodium hydrogencarbonate solution and

5 methylene chloride were added, and the solution was stirred and extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by

10 silica gel column chromatography (methylene chloride/methanol = 200/1) and then crystallized from methylene chloride-ethyl acetate to afford (R)-2-methyl-6-nitro-2-(4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenoxyethyl)-

15 2,3-dihydroimidazo[2,1-b]oxazole (3.23 g, yield 63%) as a light yellow powder.

Optical purity >99.5% e.e.

$[\alpha]_D^{28} = -8.25^\circ$ (concentration: 1.018, CHCl_3)

MS 533(M^+)

20 Melting point 213.5-217°C.

The compound of Example 159 was prepared also with the following Example 160.

Example 160

Preparation of (R)-2-methyl-6-nitro-2-(4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenoxyethyl)-

25 2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethoxybenzyl)piperazin-1-yl]phenol (3.36 g, 9.54 mmol) was dissolved in of DMF

(20 ml). To the solution, sodium hydride (420 mg, 10.5 mmol) was added at room temperature, and the solution was stirred for 15 minutes at 80°C. To the reaction mixture, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (2.18 g, 10.0 mmol) was added with cooling on ice-bath followed by stirring for further 15 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and then crystallized from methylene chloride-ethyl acetate to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole (2.0 g, yield 40%) as a light yellow powder.

Using tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate prepared in Example 143, gave tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-1,2,3,6-tetrahydropyridine-1-carboxylate prepared in Example 144, or tert-butyl (R)-4-[4-(2-methyl-6-nitro-

2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoyl]-piperazine-1-carboxylate prepared in Example 145 gave compounds of Examples 161-163 in the same manner as in Example 159.

5 Example 161

(R)-2-Methyl-6-nitro-2-{4-[1-(4-trifluoromethoxybenzyl)piperidin-4-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole

Yield 45%, melting point 186-188°C.

10 Example 162

(R)-2-Methyl-6-nitro-2-{4-[1-(4-trifluoromethoxybenzyl)-1,2,3,6-tetrahydropyridin-4-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole

Yield 61%, melting point 168-174°C.

15 Example 163

(R)-4-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoyl]-1-(4-trifluoromethoxybenzyl)piperazine

Yield 83%, melting point 155-156°C.

20 Example 164

Preparation of (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazin-1-carboxylic acid 4-trifluoromethoxybenzylamide

25 Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 148 (120 mg, 0.26 mmol) was dissolved in methylene chloride (5

ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, then added methylene chloride (2 ml) and triethylamine (2 ml). The solution was stirred at room temperature for 5 minutes and then concentrated under reduced pressure. The residue was dissolved in DMF (10 ml). To the solution, a mixture of 4-trifluoromethoxybenzylamine (125 mg, 0.65 mmol) and 1,1'-carbonyldiimidazole (110 mg, 0.68 mmol) in DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylic acid 4-trifluoromethoxybenzylamide (48 mg, yield 32%) as a white powder.

MS 558 (M-18)⁺

Melting point 166.5-168.5°C.

Example 165

Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxybenzoyl)piperazin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole

5 Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 148 (300 mg, 0.65 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 5
10 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (10 ml), triethylamine (2 ml) and 4-trifluoromethoxybenzoyl chloride (0.15 ml, 0.98 mmol). The reaction mixture was stirred at room temperature for 1 hour, then poured
15 into water, and extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by
20 silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from methylene chloride-diisopropyl ether to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxybenzoyl)piperazin-1-yl]phenoxyethyl}-
25 2,3-dihydroimidazo[2,1-b]oxazole (263 mg, yield 74%) as a white powder.

MS 547 (M⁺)

Melting point 201.5-203.2°C.

Example 166

Preparation of (R)-2-methyl-6-nitro-2-[4-(1-oxothiomorpholin-4-yl)phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole

5 (R)-2-Methyl-6-nitro-2-[4-(thiomorpholin-4-yl)phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 137 (85 mg, 0.23 mmol) was dissolved in methylene chloride (5 ml). To the solution, m-chloroperbenzoic acid (59 mg, 0.24 mmol)
 10 was added followed by stirring at room temperature for 20 minutes. The reaction mixture was diluted with methylene chloride. The solution was washed with a sodium thiosulfate solution, a saturated sodium hydrogencarbonate solution and a saturated saline
 15 solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was crystallized from methylene chloride-isopropyl ether to afford (R)-2-methyl-6-nitro-2-[4-(1-oxothiomorpholin-4-yl)phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole (59
 20 mg, yield 67%) as a white powder.

MS 392 (M⁺)

Melting point 198-200°C.

Example 167

25 Preparation of N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-(4-trifluoromethoxyphenoxy)ethylamine

A mixture of 2-chloro-1-(2-methyloxiran-2-

ylmethyl)-4-nitroimidazole prepared in Example 6 (84 mg, 0.39 mmol), N-methyl-2-(4-trifluoromethoxyphenoxy)ethylamine (100 mg, 0.43 mmol) and DMF (1 ml) was stirred at 65-70°C for 8 hours. The reaction mixture was allowed to return to room temperature, poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford a yellow oil.

The yellow oil was dissolved in DMF (1 ml). To the solution, sodium hydride (11 mg, 0.28 mmol) was added followed by stirring at room temperature for 1 hour. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from methylene chloride-diisopropyl ether to afford N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-(4-trifluoromethoxyphenoxy)ethylamine (34 mg, yield 21%) as a white powder.

Melting point 86.4-89.2°C.

Example 168

Preparation of tert-butyl N-methyl-N-{2-[N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)amino]ethyl}carbamate

- 5 A mixture of 2-chloro-4-nitro-1H-imidazole (5.97 g, 27.43 mmol), tert-butyl N-methyl-{2-[N-methyl-(2-methyloxiran-2-ylmethyl)amino]ethyl}carbamate (10.53 g, 40.76 mmol), triethylamine (0.76 ml, 5.49 mmol) and 1-propanol (60 ml) was stirred under reflux for 5
- 10 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was washed with a saturated saline
- 15 solution and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford a yellow oil.
- 20 The yellow oil was dissolved in 1,4-dioxane (200 ml). To the solution, sodium hydride (500 mg, 12.5 mmol) was added followed by stirring under reflux overnight. The reaction mixture was allowed to return to room temperature and concentrated under reduced
- 25 pressure. To the residue, ice-water was added, and the solution was extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over sodium sulfate and then filtered.

The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford tert-butyl N-methyl-N-{2-[N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)amino]ethyl}carbamate (1.94 g, yield 13%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.45 (9H, s), 1.58 (3H, s), 2.38 (3H, s), 2.57 - 2.69 (3H, m), 2.79 (3H, s), 2.89 (1H, d, J = 14.9 Hz), 3.15 - 3.25 (2H, bm), 3.85 (1H, d, J = 14.9 Hz), 4.33 (1H, br), 7.52 (1H, s).

Example 169

Preparation of (S)-N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}ethylamine

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (523 mg, 2.41 mmol) and N-methyl-2-[4-(4-trifluoromethylphenyl)-piperazin-1-yl]ethylamine (900 mg, 3.13 mmol) were added to DMF (15 ml) followed by stirring at 70-80°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene

chloride/ethyl acetate = 20/1) to afford a yellow oil.

The yellow oil was dissolved in DMF (15 ml). To the solution, sodium hydride (115 mg, 2.89 mmol) was added followed by stirring at room temperature for 1
 5 hour. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated
 10 under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from methylene chloride-diisopropyl ether to afford (S)-N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
 15 b]oxazol-2-ylmethyl)-2-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}ethylamine (173 mg, yield 15%) as a white powder.

MS 468 (M⁺)

Melting point 148.0-150.5°C.

20 Using corresponding starting materials gave compounds of Examples 170 to 177 in the same manner as in Example 169.

Example 170

(S)-N-Methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo-
 25 [2,1-b]oxazol-2-ylmethyl)-2-(4-trifluoromethyl-phenoxy)ethylamine

White powder, yield 12%

MS 399 (M-H)⁺

Melting point 123.0-126.0°C.

Example 171

(S)-N-Methyl-N-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-(4-
5 trifluoromethoxyphenoxy)ethylamine

White powder, yield 45%

MS 416(M⁺)

Melting point 112.5-115.0°C.

Example 172

10 (S)-N,N'-Dimethyl-N-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-N'-(4-
trifluoromethylphenyl)-1,2-ethylenediamine

White powder, yield 24%

MS 413(M⁺)

15 Melting point 135.5-137.5°C.

Example 173

Tert-butyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)ethyl]-
piperazine-1-carboxylate

20 White powder, yield 30%

MS 425(M+H)⁺

Melting point 149.5-151.8°C.

Example 174

(S)-N-Benzyl-N-[2-(4-trifluoromethoxyphenoxy)ethyl]-2-
25 methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
ylmethylamine

White powder, yield 25%

Melting point 96.5-97°C.

Example 175

(S)-N-Methyl-N-[3-(4-trifluoromethoxyphenoxy)propyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethanamine

5 White powder, yield 50%

Melting point 92-95°C.

Example 176

(S)-N-Methyl-N-[2-(4-chlorophenoxy)ethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethanamine

10 White powder, yield 27%

Melting point 130.5-132°C.

Example 177

(S)-N-Methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-[4-(4-trifluoromethyl-

15 phenoxy)piperidin-1-yl]ethanamine

Light brown powder, yield 26%

¹H-NMR (CDCl₃) δppm:

1.58 (3H, s), 1.70 - 1.85 (2H, m), 1.98 (2H, br), 2.37 (3H, s), 2.25 - 2.50 (4H, m), 2.50 - 2.80 (5H, m), 2.90
20 (1H, d, J = 14.9 Hz), 3.85 (1H, d, J = 9.5 Hz), 4.37 (1H, m), 4.52 (1H, d, J = 14.9 Hz), 7.42 (2H, d, J = 8.7 Hz), 7.52 (1H, s), 7.53 (2H, d, J = 8.7 Hz).

Example 178

Preparation of N-(2-ethoxycarbonylphenyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethanamine
25

A mixture of 2-chloro-4-nitro-1H-imidazole (891 mg, 6.04 mmol), 1-(2-methyloxiran-2-ylmethyl)-1H-benzo[d][1,3]oxazin-2,4-dione (1.41 g, 6.04 mmol),

sodium acetate (545 mg, 6.64 mmol) and ethanol (10 ml) was stirred under reflux for 10 hours. The reaction mixture was allowed to return to room temperature, and concentrated under reduced pressure. To the residue, 5 water was added, and the solution was extracted with methylene chloride. The organic phase was washed with a saturated saline solution and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue 10 was dissolved in 1,4-dioxane (20 ml). To the solution, sodium hydride (219 mg, 5.48 mmol) was added followed by stirring under reflux for 5 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, 15 ice-water was added, and the precipitates were filtered off, which were purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford N-(2-ethoxycarbonylphenyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamine 20 (1.15 g, yield 55%) as a white powder. Melting point 162.5-163.2°C.

Example 179

Preparation of (S)-1-[2-hydroxy-3-(N-methyl-benzyl-amino)-2-methylpropyl]-2-chloro-4-nitroimidazole

25 A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (500 mg, 2.3 mmol), N-methylbenzylamine (334 mg, 2.76 mmol) and DMF (2.5 ml) was stirred at 60°C for 9 hours.

The reaction mixture was allowed to return to room temperature and added water followed by extraction with ethyl acetate twice. The organic phases were combined, washed with water three times, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford (S)-1-[2-hydroxy-3-(N-methyl-N-benzylamino)-2-methylpropyl]-2-chloro-4-nitroimidazole (712 mg, yield 91%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 2.37 - 2.57 (5H, m), 3.51 (1H, d, J = 12.9 Hz), 3.72 (1H, d, J = 12.9 Hz), 3.85 (2H, s), 7.16 - 7.39 (5H, m), 7.87 (1H, s).

Using corresponding starting materials gave compounds of Examples 180 to 187 in the same manner as in Example 179.

Example 180

(S)-1-{2-Hydroxy-3-[N-methyl-(3-chlorobenzyl)]amino-2-methyl}propyl-2-chloro-4-nitroimidazole

Yield 98%

¹H-NMR (CDCl₃) δppm:

1.15 (3H, s), 2.35 - 2.57 (5H, m), 3.53 (1H, d, J = 13.3 Hz), 3.67 (1H, d, J = 13.3 Hz), 3.92 (2H, s), 7.10 - 7.31 (4H, m), 7.95 (1H, s).

Example 181

(S)-1-{2-Hydroxy-3-(N-methyl-4-chlorobenzylamino)-2-

methylpropyl]-2-chloro-4-nitroimidazole

Yield 86%

¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 2.33 - 2.59 (5H, m), 3.53 (1H, d, J =
 5 13.2 Hz), 3.68 (1H, d, J = 13.2 Hz), 3.92 (2H, s), 7.19
 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.96
 (1H, s).

Example 182

(S)-1-[2-Hydroxy-3-(N-methyl-4-trifluoromethoxybenzyl-
 10 amino)-2-methylpropyl]-2-chloro-4-nitroimidazole

Yield 98%

¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 2.37 (3H, s), 2.47 (1H, d, J = 13.9 Hz),
 2.58 (1H, d, J = 13.9 Hz), 3.58 (1H, d, J = 13.3 Hz),
 15 3.72 (1H, d, J = 13.3 Hz), 3.94 (2H, s), 7.19 (2H, d, J
 = 8.6 Hz), 7.31 (2H, d, J = 8.6 Hz), 7.99 (1H, s).

Example 183

(S)-1-[2-Hydroxy-3-(N-methyl-4-trifluoromethylbenzyl-
 amino)-2-methylpropyl]-2-chloro-4-nitroimidazole

20 Yield 100%

¹H-NMR (CDCl₃) δppm:

1.15 (3H, s), 2.38 (3H, s), 2.50 (1H, d, J = 13.9 Hz),
 2.60 (1H, d, J = 13.9 Hz), 3.65 (1H, d, J = 13.6 Hz),
 3.79 (1H, d, J = 13.6 Hz), 3.97 (2H, s), 7.41 (2H, d, J
 25 = 8.2 Hz), 7.61 (2H, d, J = 8.2 Hz), 8.00 (1H, s).

Example 184

(S)-1-[2-Hydroxy-3-(N-methyl-4-methoxybenzylamino)-2-

methylpropyl]-2-chloro-4-nitroimidazole

Yield 85%

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 2.36 - 2.50 (5H, m), 3.45 (1H, d, J =
5 12.8 Hz), 3.64 (1H, d, J = 12.8 Hz), 3.80 (3H, s), 3.84
(2H, s), 6.84 (2H, dd, J = 1.9 Hz, 8.6 Hz), 7.13 (2H,
dd, J = 1.9 Hz, 8.6 Hz), 7.89 (1H, s).

Example 185

(S)-1-[2-Hydroxy-3-(N-methyl-4-dimethylaminobenzyl-
10 amino)-2-methylpropyl]-2-chloro-4-nitroimidazole

Yield 94%

¹H-NMR (CDCl₃) δppm:

1.11 (3H, s), 2.34 - 2.47 (5H, m), 2.93 (s, 6H), 3.39
(1H, d, J = 12.8 Hz), 3.60 (1H, d, J = 12.8 Hz), 3.81
15 (2H, s), 6.65 (2H, d, J = 8.7 Hz), 7.03 (2H, d, J = 8.7
Hz), 7.87 (1H, s).

Example 186

(S)-1-[2-Hydroxy-3-(N-methyl-phenylamino)-2-
methylpropyl]-2-chloro-4-nitroimidazole

20 Yield 92%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 3.06 (3H, s), 3.40 (2H, s), 4.05 (1H, d,
J = 14.2 Hz), 4.13 (1H, d, J = 14.2 Hz), 6.74 - 6.89
(3H, m), 7.17 - 7.34 (2H, m), 8.04 (1H, s).

25

Example 187

(S)-1-[2-Hydroxy-3-(N-methyl-4-chlorophenylamino)-2-
methylpropyl]-2-chloro-4-nitroimidazole

Yield 92%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 3.04 (3H, s), 3.38 (2H, s), 4.08 (2H, s),
6.74 (2H, dd, J = 2.1 Hz, 7.2 Hz), 7.19 (2H, dd, J =
2.1 Hz, 7.2 Hz), 8.02 (1H, s).

5 Example 188

Preparation of (S)-2-(N-benzyl-N-methyl)aminomethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

To a mixture of (S)-1-[2-hydroxy-3-(N-methyl-benzylamino)-2-methylpropyl]-2-chloro-4-nitroimidazole
10 prepared in Example 179 (710 mg, 2.1 mmol) and DMF (2.1 ml), sodium hydride (101 mg, 2.51 mmol) was added followed by stirring for 2 hours with cooling on ice-bath. To the reaction mixture, ethylacetate (0.7 ml) and water (5 ml) were added in this order. The
15 precipitates were filtered off and dissolved in isopropyl alcohol (10 ml) with stirring under reflux. To the solution, activated carbon(28 mg) was added followed by stirring under reflux for 20 minutes. After filtration, isopropyl ether (3 ml) was added to
20 the solution, and the mixture was allowed to stand. The precipitates were collected to afford (S)-2-(N-benzyl-N-methyl)aminomethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (248 mg, yield 39%) as a yellow powder.
25 Melting point 132.5-133°C.

Using corresponding starting materials gave compounds of Examples 189 to 196 in the same manner as in Example 188.

Example 189

(S)-2-[N-(4-Chlorobenzyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 44%, melting point 129-129.5°C.

5 Example 190

(S)-2-[N-(3-Chlorobenzyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 65%, melting point 177.5-178.5°C.

Example 191

10 (S)-2-[N-(4-Trifluoromethoxybenzyl)-N-methylamino]-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 53%, melting point 145-146°C.

Example 192

15 (S)-2-[N-(4-Trifluoromethylbenzyl)-N-methylamino]-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 49%, melting point 130-132°C.

Example 193

20 (S)-2-[N-(4-Methoxybenzyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 59%, melting point 144-147°C.

Example 194

(S)-2-[N-(4-Dimethylaminobenzyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
25 Yield 47%, melting point 168-169°C.

Example 195

(S)-2-(N-Phenyl-N-methylamino)methyl-2-methyl-6-nitro-

2,3-dihydroimidazo[2,1-b]oxazole

Yield 55%, melting point 147-148°C.

Example 196

(S)-2-[N-(4-Chlorophenyl)-N-methylamino]methyl-2-

5 methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 34%, melting point 174-175°C.

Example 197

Preparation of 4-trifluoromethylbenzyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

10 b]oxazol-2-ylmethylamino)ethyl]piperazine-1-carboxylate

Tert-butyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)-ethyl]piperazine-1-carboxylate prepared in Example 173 (300 mg, 0.71 mmol) was dissolved in methylene chloride
15 (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (2 ml) and triethylamine (2 ml). After stirring for 5 minutes
20 at room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in DMF (15 ml). To the solution, a mixture of 4-trifluoromethylbenzyl alcohol (373 mg, 2.12 mmol) and 1,1'-carbonyldiimidazole (344 mg, 2.12 mmol) in DMF (5
25 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was

washed with a saturated saline solution and dried over magnesium sulfate. After filtration, the resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

5 chromatography (methylene chloride/methanol = 50/1) and crystallized from methylene chloride-isopropyl ether to afford 4-trifluoromethylbenzyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)ethyl]piperazine-1-carboxylate (196 mg,
10 yield 53%) as a white powder.

MS 509(M-H₂O)⁺

Melting point 77.2-76.9°C.

Example 198

Preparation of (S)-N-methyl-N-(2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethylamine

Tert-butyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)-ethyl]piperazine-1-carboxylate prepared in Example 173
20 (400 mg, 0.94 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (2 ml)
25 and triethylamine (2 ml). After stirring for 5 minutes at room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in methanol (10 ml). To the solution, 4-(trifluoro-

methyl)benzaldehyde (0.4 ml, 2.83 mmol), sodium cyanotrihydroborate (178 mg, 2.83 mmol) and acetic acid (0.2 ml) were added followed by stirring at room temperature for 30 minutes. To the solution, a
5 saturated sodium hydrogencarbonate solution and methylene chloride were added followed by stirring, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate. After filtration, the resulting filtrate was concentrated
10 under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford (S)-N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
15 b]oxazol-2-ylmethyl)-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethylamine (307 mg, yield 68%) as a white powder.
MS 482 (M⁺)
Melting point 102.0-104.5°C.

20

Example 199

Preparation of ethyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

2,4-Dinitro-1H-imidazole (0.678 g, 3.92 mmol) and phenyl oxiran-2-ylmethylcarbamate (1.04 g, 5.87
25 mmol) were dissolved in ethanol (20 ml). To the solution, sodium acetate (0.386 g, 4.70 mmol) was added followed by stirring under reflux overnight. To the reaction mixture, a saturated sodium hydrogencarbonate

solution and methylene chloride were added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) and treated with diisopropyl ether to afford ethyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate (0.116 g, yield 11.6%) as a light brown solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

1.15 (3H, t, $J = 7.1$ Hz), 3.41 - 3.51 (2H, m), 3.93 - 4.11 (3H, m), 4.38 (1H, dd, $J = 8.6$ Hz, 10.7 Hz), 5.31 - 5.47 (1H, m), 7.52 (1H, br), 8.13 (1H, s).

Example 200

Preparation of benzyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

2,4-Dinitro-1H-imidazole (3 g, 19 mmol) and benzyl (2-methyloxiran-2-ylmethyl)carbamate (4.31 g, 19 mmol) were dissolved in ethanol (20 ml). To the solution, sodium acetate (1.56 g, 19.0 mmol) was added followed by stirring at 70°C overnight. To the reaction mixture, a saturated sodium hydrogencarbonate solution and methylene chloride were added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column

chromatography (n-hexane/ethyl acetate = 1/1, methylene chloride/methanol = 50/1) and recrystallized from ethyl acetate-methylene chloride to afford benzyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

5 ylmethyl)carbamate (0.298 g, yield 4.7%) as a colorless solid.

Melting point 171.3-172.2°C

¹H-NMR (DMSO-d₆) δppm:

1.55 (3H, s), 3.46 (2H, d, J = 6.3 Hz), 4.06 (1H, d, J
10 = 11.0 Hz), 4.25 (1H, d, J = 11.0 Hz), 5.03 (2H, s),
7.19 - 7.41 (5H, m), 7.76 (1H, t, J = 6.3 Hz), 8.13
(1H, s).

Example 201

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
15 b]oxazol-2-ylmethylamine trifluoroacetate

A mixture of benzyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate prepared in Example 200 (190 mg, 0.57 mmol), trifluoroacetic acid (4 ml) and methylene chloride (5 ml) was
20 stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. To the residue was treated with diethyl ether to afford 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamine trifluoroacetate (120 mg, yield 67%) as a
25 light yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.35 (3H, s), 3.23 (1H, d, J = 9.6 Hz), 3.49 (1H, d, J
= 9.6 Hz), 3.82 - 3.98 (2H, m), 7.98 (1H, s), 12.22

(1H, s).

Using corresponding starting materials gave compounds of Examples 202 to 204 in the same manner as in Example 200.

5 Example 202

Benzyl N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 14%, melting point 150.3-151.6°C.

 Example 203

10 Benzyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 11%

¹H-NMR (DMSO-d₆) δppm:

3.45 - 3.59 (2H, m), 4.07 (1H, dd, J = 6.6 Hz, 10.8
15 Hz), 4.39 (1H, dd, J = 8.6 Hz, 10.8 Hz), 5.04 (2H, s),
5.32 - 5.50 (1H, m), 7.23 - 7.41 (5H, m), 7.71 (1H,
br), 8.13 (1H, s).

 Example 204

20 Tert-butyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 27%

¹H-NMR (CDCl₃) δppm:

1.43 (9H, s), 3.65 (2H, dd, J = 4.3 Hz, 6.2 Hz), 4.20
(1H, dd, 7.0 Hz, 10.5 Hz), 4.36 (1H, dd, J = 8.6 Hz,
25 10.5 Hz), 5.20 (1H, t, J = 6.2 Hz), 5.35 - 5.48 (1H,
m), 7.56 (1H, s).

 Example 205

Preparation of 4-chlorobenzyl (2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

2,4-Dinitro-1H-imidazole (0.518 g, 3.28 mmol)
and 4-chlorobenzyl (2-methyloxiran-2-ylmethyl)carbamate
(2.097 g, 8.20 mmol) and sodium acetate (0.538 g, 6.56
5 mmol) in ethanol (6 ml) was stirred under reflux for 1
hour. To the solution, water was added and the
precipitates were filtered off. The resulting solid
was treated with diethyl ether to afford 4-chlorobenzyl
(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
10 ylmethyl)carbamate (0.197 g, yield 16%) as a colorless
solid.

Melting point 221.0-221.8°C.

Using benzyl N-methyl-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate
15 prepared in Example 202 gave the compound of Example
206 in the same manner as in Example 201.

Example 206

N-Methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazol-2-ylmethylaniline trifluoroacetate

20 Melting point 176.2-178.8°C.

Using corresponding starting materials gave
compounds of Examples 207 to 211 in the same manner as
in Example 205.

Example 207

25 4-Fluorobenzyl (2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate
Yield 25%, melting point 200.4-202.1°C.

Example 208

Ethyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 26%, melting point 182.5-183.4°C.

Example 209

5 4-Trifluoromethoxybenzyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 17%, melting point 182.3-184.4°C.

Example 210

10 4-Chlorobenzyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 17%, melting point 182.6-182.9°C.

Example 211

15 4-Fluorobenzyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 17%, melting point 164.6-165.1°C.

Example 212

Preparation of 4-fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-N-methylcarbamate

20 2-Chloro-4-nitro-1H-imidazole (0.953 g, 6.46 mmol) and 4-fluorobenzyl N-methyl-(2-methyloxiran-2-ylmethyl)carbamate (1.964 g, 7.75 mmol) were dissolved in ethanol (20 ml). To the solution, sodium acetate (0.583 g, 7.11 mmol) was added followed by stirring
25 under reflux overnight. The reaction mixture was concentrated under reduced pressure. To the residue, ethyl acetate and water were added, and the solution was extracted with ethyl acetate. The organic phase

was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford
 5 4-fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-N-methylcarbamate (1.683 g, yield 65%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.17 (3H, s), 3.06 (3H, s), 3.25 (1H, d, J = 14.7 Hz),
 10 3.51 (1H, d, J = 14.7 Hz), 4.00 (2H, s), 5.12 (2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m), 8.07 (1H, s).

Using 4-fluorobenzyl N-methyl-(oxiran-2-yl-methyl)carbamate gave the compound of Example 213 in the same manner as in Example 212.

15 Example 213

4-Fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]-N-methylcarbamate

Yield 51%

¹H-NMR (CDCl₃) δppm:

20 3.04 (3H, s), 3.27 - 3.55 (2H, m), 3.73 - 4.23 (4H, m), 5.11 (2H, s), 7.00 - 7.14 (2H, m), 7.27 - 7.41 (2H, m), 7.96 (1H, s).

Example 214

Preparation of 4-fluorobenzyl N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate
 25

4-Fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-N-methylcarbamate

prepared in Example 212 (1.683 g, 4.20 mmol) was dissolved in 1,4-dioxane (30 ml). To the solution, sodium hydride (0.185 g, 4.62 mmol) was added followed by stirring at room temperature for 1 hour and then
5 stirred under reflux for 7 hours. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the precipitates were filtered off and purified by silica gel column chromatography (n-hexane/acetone = 2/1). The resulting
10 solid was treated with a mixture of n-hexane and ethyl acetate to afford 4-fluorobenzyl N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate (0.381 g, yield 25%) as a colorless solid.

15 Melting point 168.9-169.9°C.

Using 4-fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]-N-methylcarbamate prepared in Example 213 gave the compound of Example 215 in the same manner as in Example 214.

20 Example 215

4-Fluorobenzyl N-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylcarbamate

Yield 16%, melting point 124.5-128.1°C.

Using corresponding starting materials gave
25 compounds of Examples 216 to 220 in the same manner as in Example 179.

Example 216

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-{[1-(4-

chlorophenyl)piperidin-4-yl]-N-methylamino}-2-hydroxy-2-methylpropane

Yellow oil, yield 98%

¹H-NMR (CDCl₃) δppm:

- 5 1.13 (3H, s), 1.57 - 1.82 (4H, m), 2.38 - 2.71 (4H, m), 2.40 (3H, m), 3.65 - 3.71 (2H, m), 3.82 (1H, s), 3.89 - 4.01 (2H, m), 6.81 - 6.86 (2H, m), 7.16 - 7.22 (2H, m), 8.06 (1H, s).

Example 217

- 10 (S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-{[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]-N-methylamino}-2-hydroxy-2-methylpropane

Yellow oil, yield 91%

¹H-NMR (CDCl₃) δppm:

- 15 1.13 (3H, s), 1.59 - 1.83 (4H, m), 2.41 (3H, s), 2.43 - 2.73 (5H, m), 3.66 - 3.73 (2H, m), 3.84 (1H, s), 3.93 (1H, d, J = 14.2 Hz), 4.00 (1H, d, J = 14.2 Hz), 6.86 - 6.91 (2H, m), 7.07 - 7.12 (2H, m), 8.06 (1H, s).

Example 218

- 20 (S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-{[1-(4-trifluoromethylphenyl)piperidin-4-yl]-N-methylamino}-2-hydroxy-2-methylpropane

Yellow oil, yield 96%

¹H-NMR (CDCl₃) δppm:

- 25 1.13 (3H, s), 1.54 - 1.70 (2H, m), 1.77 - 1.84 (2H, m), 2.40 (3H, s), 2.42 - 2.60 (3H, m), 2.72 - 2.82 (2H, m), 3.79 (1H, s), 3.84 - 3.89 (2H, m), 3.92 (1H, d, J = 14.2 Hz), 3.99 (1H, d, J = 14.2 Hz), 6.91 (2H, d, J =

8.7 Hz), 7.46 (2H, d, $J = 8.7$ Hz), 8.06 (1H, s).

Example 219

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-([1-(4-cyanophenyl)piperidin-4-yl]-N-methylamino)-2-hydroxy-2-methylpropane

Yellow oil, yield 89%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.13 (3H, s), 1.51 - 1.65 (2H, m), 1.77 - 1.84 (2H, m),
2.39 (3H, s), 2.42 - 2.62 (3H, m), 2.76 - 2.88 (2H, m),
10 3.75 (1H, s), 3.88 - 4.03 (4H, m), 6.81 - 6.88 (2H, m),
7.45 - 7.53 (2H, m), 8.05 (1H, s).

Example 220

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-([1-(tert-butoxycarbonyl)piperidin-4-yl]-N-methylamino)-2-hydroxy-2-methylpropane

Yellow oil

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.11 (3H, s), 1.46 (9H, s), 1.50 - 1.80 (4H, m), 2.37
(3H, s), 2.40 - 2.75 (5H, m), 3.90 (1H, d, $J = 14.2$
20 Hz), 3.99 (1H, d, $J = 14.2$ Hz), 4.22 (2H, br), 8.05
(1H, s).

Using compounds prepared in Examples 216 to 220 gave compounds of Examples 221 to 225 in the same manner as in Example 188.

Example 221

(S)-2-([1-(4-Chlorophenyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

White powder, yield 47%

MS 406(M+1)⁺

Melting point 179.2-182.1°C.

Example 222

- 5 (S)-2-([1-(4-Trifluoromethoxyphenyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 127.2-129.7°C.

Example 223

- 10 (S)-2-([1-(4-Trifluoromethylphenyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 131.5-133.6°C.

Example 224

- 15 (S)-2-([1-(4-Cyanophenyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 149-152°C.

Example 225

- 20 (S)-2-([1-(Tert-butoxycarbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Light yellow powder, yield 37%
Melting point 138.5-140.3°C.

- 25 Example 226

Preparation of (S)-2-([1-(4-trifluoromethylbenzyloxy-carbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

(S)-2-([1-(Tert-butoxycarbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 225 (400 mg, 1.01 mmol) was dissolved in methylene chloride (1 ml). To the solution, trifluoroacetic acid (1 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene (1 ml) chloride and triethylamine (2 ml). The solution was stirred at room temperature for 5 minutes and then concentrated under reduced pressure, and the residue was dissolved in DMF (8 ml). To the solution, a mixture of 4-(trifluoromethyl)benzyl alcohol (267 mg, 1.51 mmol) and 1,1'-carbonyldiimidazole (246 mg, 1.51 mmol) in DMF (2 ml) stirred at room temperature for 4 hours was added followed by stirring at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford (S)-2-([1-(4-trifluoromethyl-benzyloxycarbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (341 mg, yield 68%) as a light yellow powder.

Melting point 110.6-113.1°C.

Using corresponding starting materials gave compounds of Examples 227 and 228 in the same manner as in Example 226.

5 Example 227

(S)-2-([1-(4-Trifluoromethoxybenzyloxycarbonyl)-piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 84.2-86.8°C.

10 Example 228

(S)-2-([1-(4-Chlorobenzyloxycarbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 116.2-116.6°C.

15 Example 229

Preparation of 2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzyloxy)piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-
20 nitroimidazole prepared in Example 6 (122 mg, 0.56 mmol) and 4-[4-(trifluoromethyl)benzyloxy]piperidine (188 mg, 4.86 mol) were dissolved in DMF (10 ml) followed by stirring at 70-75°C for 5 hours. The reaction mixture was allowed to return to room
25 temperature, poured into water, extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under

reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford a yellow oil.

The yellow oil was dissolved in DMF (10 ml).

5 To the solution, sodium hydride (134 mg, 3.36 mmol) was added with cooling on ice-bath, and the solution was stirred at room temperature for 1 hour. The reaction mixture was poured into water, extracted with ethyl acetate. The organic phase was washed with a saturated
10 saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from ethyl acetate-diisopropyl
15 ether to afford 2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzyloxy)piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (41 mg, yield 17%) as a white powder.

MS 440 (M-1)⁺

20 ¹H-NMR (CDCl₃) δppm:

1.45 - 1.70 (2H, m), 1.60 (3H, s), 1.75 - 1.88 (2H, m),
2.26 - 2.40 (1H, m), 2.45 - 2.55 (2H, m), 2.72 - 2.95
(3H, m), 3.38 (1H, m), 3.89 (1H, d, J = 9.6 Hz), 4.31
(1H, d, J = 9.6 Hz), 4.54 (2H, s), 7.43 (2H, d, J = 8.2
25 Hz), 7.53 (1H, s), 7.79 (2H, d, J = 8.2 Hz).

Example 230

Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-

yl]propan-2-ol

To a solution of 2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole prepared in Example 5 (0.30 g, 0.77 mmol) and 4-(4-trifluoromethylphenoxy)piperidine (0.21 g, 0.85 mmol) in DMF (6 ml), sodium iodide (0.13 g, 0.77 mmol) and triethylamine (0.12 ml, 0.77 mmol) were added followed by stirring at 80°C for 7 hours. To the reaction mixture, water was added, and the resulting solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]propan-2-ol (0.23 g, yield 63%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.14 (3H, s), 1.76 - 2.04 (4H, m), 2.36 (1H, d, J = 14.0 Hz), 2.43 - 2.72 (3H, m), 2.76 - 3.00 (2H, m), 3.46 - 3.52 (1H, br), 3.98 (2H, s), 4.37 - 4.50 (1H, m), 6.91 - 7.00 (2H, m), 7.48 - 7.61 (2H, m), 8.05 (1H, s).

Using corresponding starting materials gave the compound of Example 231 in the same manner as in Example 230.

Example 231

1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-

trifluoromethoxyphenoxy)piperidin-1-yl]propan-2-ol

Yield 61%

¹H-NMR (CDCl₃) δppm:

1.14 (3H, s), 1.74 - 2.04 (4H, m), 2.35 (1H, d, J =
 5 13.9 Hz), 2.40 (1H, d, J = 13.9 Hz), 2.43 - 2.70 (2H,
 m), 2.74 - 3.00 (2H, m), 3.98 (2H, s), 4.25 - 4.41 (1H,
 m), 6.86 - 6.92 (2H, m), 7.11 - 7.15 (2H, m), 8.05 (1H,
 s).

Example 232

10 Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-2-
 methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-
 yl]propan-2-ol

A solution of 2-chloro-1-(2-methyloxiran-2-
 ylmethyl)-4-nitroimidazole prepared in Example 6 (0.3
 15 g, 1.38 mmol) and N-(piperidin-4-yl)-4-trifluoro-
 methoxyaniline (0.43 g, 1.66 mmol) in DMF (8 ml) was
 stirred at 80°C for 2 hours. To the reaction mixture,
 water was added, and the solution was extracted with
 ethyl acetate, dried over magnesium sulfate and then
 20 concentrated under reduced pressure. The residue was
 purified by silica gel column chromatography (n-
 hexane/ethyl acetate = 1/1) to afford 1-(2-chloro-4-
 nitroimidazol-1-yl)-2-methyl-3-[4-(4-
 trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol
 25 (0.37 g, yield 56%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 1.39 - 1.63 (2H, m), 1.96 - 2.09 (2H, m),
 2.47 (1H, d, J = 13.9 Hz), 2.43 - 2.63 (3H, m), 2.67 -

2.83 (1H, m), 2.87 - 3.02 (1H, m), 3.15 - 3.39 (1H, m),
3.41 - 3.72 (2H, m), 3.97 (2H, s), 6.46 - 6.59 (2H, m),
6.96 - 7.09 (2H, m), 8.05 (1H, s).

Example 233

- 5 Preparation of 2-methyl-6-nitro-2-[4-(4-trifluoro-
methylphenoxy)piperidin-1-ylmethyl]-2,3-
dihydroimidazo[2,1-b]oxazole

To a solution of 1-(2-chloro-4-nitroimidazol-
1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)-
10 piperidin-1-yl]propan-2-ol prepared in Example 230 (225
mg, 0.49 mmol) in DMF (2.5 ml), sodium hydride (23 mg,
0.59 mmol) was added followed by stirring for 1 hour
with cooling on ice-bath. To the reaction mixture,
ice-water and ethyl acetate were added. The
15 precipitates were filtered off, washed with water,
recrystallized from methylene chloride-diisopropyl
ether and then washed with n-hexane to afford 2-methyl-
6-nitro-2-[4-(4-trifluoromethylphenoxy)piperidin-1-
ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (80 mg,
20 yield 39%) as a light yellow solid.
Melting point 113-114°C.

Using corresponding starting materials gave
the compound of Example 234 in the same manner as in
Example 233.

- 25 Example 234

2-Methyl-6-nitro-2-[4-(4-trifluoromethoxyphenoxy)-
piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 117-119°C.

Example 235

Preparation of 2-[4-(4-trifluoromethoxyphenyl)-aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

5 Using 1-(2-chloro-4-nitro-imidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol prepared in Example 233 (369 mg, 0.77 mmol) gave 2-[4-(4-trifluoromethoxy-phenylamino)piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-
10 dihydroimidazo[2,1-b]oxazole (25 mg, yield 7%) as a yellow powder in the same manner as in Example 232.

MS 441(M⁺)

¹H-NMR (CDCl₃) δppm:

1.11 - 1.40 (2H, m), 1.61 (3H, s), 1.85 - 2.01 (2H, m),
15 2.37 (1H, dt, J = 2.7 Hz, 11.4 Hz), 2.46 - 2.59 (2H, m), 2.76 - 2.84 (1H, m), 2.87 (1H, d, J = 14.9 Hz),
2.95 - 3.03 (1H, m), 3.10 - 3.25 (1H, m), 3.50 (1H, d, J = 7.8 Hz), 3.90 (1H, d, J = 9.7 Hz), 4.29 (1H, d, J = 9.7 Hz), 6.46 - 6.52 (2H, m), 6.98 - 7.01 (2H, m), 7.50
20 (1H, s).

Example 236

Preparation of tert-butyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

2-Chloro-4-nitro-1H-imidazole (1.08 g, 7.31 mmol), tert-butyl N-methyl-[1-(2-methyloxiran-2-ylmethyl)piperidin-4-yl]carbamate (2.08 g, 7.31 mmol) and

sodium acetate (660 mg, 8.04 mmol) in 1-propanol (15 ml) were stirred under reflux overnight. The reaction mixture was concentrated under reduced pressure. The residue was added water, and the mixture was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1), crystallized from methylene chloride-isopropyl ether to afford tert-butyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate (348 mg, yield 12%) as a white powder. MS 396(M+1)⁺

Melting point 198.8-201.1°C.

Example 237

Preparation of benzyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Tert-butyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 236 (207 mg, 0.52 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene chloride (5 ml), triethylamine (1 ml) and benzyl chlorocarbonate (0.15

ml, 1.05 mmol) were added followed by stirring at room temperature for 30 minutes. The reaction mixture was poured into water, extracted with methylene chloride. The organic phase was dried over sodium sulfate and
5 then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from ethyl acetate-isopropyl ether to afford benzyl N-methyl-[1-
10 (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate (184 mg, yield 82%) as a white powder.

MS 430 (M+H)⁺

Melting point 138.7-139.2°C.

15 Using 4-chlorobenzyl chlorocarbonate gave the compound of Example 238 in the same manner as in Example 237. Also, using 4-chlorophenylacetyl chloride gave the compound of Example 239 in the same manner as in Example 237.

20

Example 238

4-Chlorobenzyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

25 Melting point 147.2-149.2°C.

Example 239

2-(4-[N-(4-Chlorophenylacetyl)-N-methyl]aminopiperidin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazole

Melting point 206.8-208°C.

Example 240

Preparation of 2-methyl-2-{4-[N-methyl-N-(4-trifluoro-
5 methoxyphenyl)]aminopiperidin-1-yl}methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

To a solution of 2-[4-(4-trifluoromethoxy-
phenyl)aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole prepared in Example 235
10 (60 mg, 0.14 mmol) in methanol (2 ml), a 37%
formaldehyde solution (51 µl, 0.70 mmol) and sodium
cyanotrihydroborate (26 mg, 0.42 mmol) were added
followed by stirring at room temperature for further 30
minutes. To the reaction mixture, acetic acid (23 µl,
15 0.42 mmol) was added followed by stirring at room
temperature for 1 hour with cooling on ice-bath. To
the reaction mixture, a sodium hydrogencarbonate
solution was added, and the mixture was extracted with
methylene chloride. The organic phase was dried over
20 magnesium sulfate and then concentrated under reduced
pressure. The residue was purified by silica gel
column chromatography (methylene chloride/ethyl acetate
= 1/1) and crystallized from diisopropyl ether to
afford 2-methyl-2-{4-[N-methyl-N-(4-
25 trifluoromethoxyphenyl)]aminopiperidin-1-yl}methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazole (40 mg, yield
65%) as a light yellow solid.
Melting point 135-136°C.

Example 241

Preparation of 2-[4-(4-chlorobenzyl)oxypiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

- 5 A mixture of 2-chloro-4-nitro-1H-imidazole (1.5 g, 10.17 mmol), 4-(4-chlorobenzyloxy)-1-(2-methyloxiran-2-ylmethyl)piperidine (2.5 g, 8.45 mmol), sodium hydrogencarbonate (0.86 g, 10.24 mmol) and ethanol (15 ml) was stirred under reflux for 15 hours.
- 10 The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then concentrated
- 15 under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) to afford 2-[4-(4-chlorobenzyl)oxypiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (662 mg, yield 16%) as
- 20 a white powder.

Melting point 129-130°C.

Example 242

- Preparation of 2-{4-[N-(4-chlorophenyl)-N-methyl]amino-piperidin-1-yl}methyl-2-methyl-6-nitro-2,3-
- 25 dihydroimidazo[2,1-b]oxazole

A mixture of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (350 mg, 1.61 mmol), 4-[N-(4-chlorophenyl)-N-methylamino]-

piperidine (373 mg, 1.66 mmol) and DMF (15 ml) was stirred at 70°C for 5 hours. To the reaction mixture, sodium hydride (77 mg, 1.93 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. The
5 reaction mixture was poured into ice-water and extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, washed with a saturated saline solution, dried over sodium sulfate and then concentrated under reduced pressure.
10 The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 1/1) to afford 2-{4-[N-(4-chlorophenyl)-N-methyl]aminopiperidin-1-yl}methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (307 mg, yield 47%) as a
15 light yellow powder.

Melting point 186-187.8°C.

Using 4-(4-trifluoromethoxybenzyl)piperidine, 4-(4-trifluoromethylbenzyl)piperidine, 4-(4-chlorobenzyl)piperidine and 4-(chlorobenzoyl)piperidine gave
20 compounds of Examples 243 to 246 in the same manner as in Example 242.

Example 243

2-Methyl-6-nitro-2-[4-(4-trifluoromethoxybenzyl)-piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole
25 Melting point 143.5-145°C.

Example 244

2-Methyl-6-nitro-2-[4-(4-trifluoromethylbenzyl)-piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 125-126°C.

Example 245

2-[4-(4-Chlorobenzyl)piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

5 Melting point 109-110.5°C

Example 246

2-[4-(4-Chlorobenzoyl)piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 165-167°C.

10 Example 247

Preparation of 2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzoyl)piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (80 mg, 0.37 mmol), 4-(4-trifluoromethylbenzoyl)piperidine (95 mg, 0.37 mmol), sodium acetate (150 mg, 1.83 mmol) and DMF (2 ml) was stirred at 80°C overnight. The reaction mixture was poured into water, and extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, washed with a saturated saline solution, dried over sodium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to afford 2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzoyl)piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole (46 mg, yield 29%) as a

white powder.

Melting point 172-174°C.

Using corresponding starting materials gave the compound of Example 248 in the same manner as in
5 Example 247.

Example 248

2-Methyl-6-nitro-2-[4-(4-trifluoromethoxybenzoyl)-
piperidin-1-yl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 165-167°C.

10 Example 249

Preparation of (S)-2-[4-(3,4-dichlorobenzyloxy)-
piperidin-1-ylmethyl]-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-
15 nitroimidazole prepared in Example 12 (396 mg, 1.82
mmol) and 4-(3,4-dichlorobenzyloxy)piperidine (614 mg,
2.36 mol) in DMF (15 ml) were stirred at 70-75°C for 4
hours. The reaction mixture was allowed to return to
room temperature, poured into water, extracted with
20 ethyl acetate. The organic phase was washed with a
saturated saline water, dried over magnesium sulfate
and then filtered. The filtrate was concentrated under
reduced pressure. The residue was purified by silica
gel column chromatography (methylene chloride/methanol
25 = 50/1) to afford a yellow oil.

The yellow oil was dissolved in DMF (15 ml).
To the solution, sodium hydride (87 mg, 2.18 mmol) was
added with cooling on ice-bath followed by stirring at

room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with a saturated saline solution, dried over magnesium sulfate and then
5 filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from methylene chloride-diisopropyl ether to afford (S)-2-[4-(3,4-
10 dichlorobenzoyloxy)piperidin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (431 mg, yield 44%) as a white powder.

MS 441 (M^+)

Melting point 132.0-136.0°C.

15 Example 250

Preparation of (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-(4-trifluoromethoxyphenyl)methanone

 Using (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (1.0
20 g, 4.6 mmol) and 4-(4-trifluoromethoxybenzoyl)piperidine (1.3 g, 4.8 mmol) gave (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-(4-
25 trifluoromethoxyphenyl)methanone (771 mg, yield 37%) as a light yellow powder.

Melting point 113.0-115.0°C.

 Example 251

Preparation of ethyl (S)-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-carboxylate

2-Chloro-4-nitro-1H-imidazole (3.7 g, 25.1 mmol), ethyl (S)-1-(2-methyloxiran-2-ylmethyl)-piperidine-4-carboxylate (4.8 g, 21.1 mmol) and sodium hydrogencarbonate (2.2 g, 25.1 mmol) in ethanol (25 ml) were stirred under reflux overnight. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) and crystallized from diethyl ether to afford ethyl (S)-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidine-4-carboxylate (1.4 g, yield 20%) as a white powder.

Melting point 101.0–103.0°C.

Example 252

Preparation of (S)-2-methyl-6-nitro-2-[4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

4-(4-Trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine (0.985 g, 4.05 mmol) and (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole

prepared in Example 12 (0.839 g, 3.86 mmol) were added to DMF (15 ml), and the solution was stirred at 60°C for 8 hours. The reaction mixture was added water and extracted with ethyl acetate. The organic phases was washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford as oil. The oil was dissolved in DMF (20 ml), and sodium hydride (94 mg, 2.35 mmol) was added with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford (S)-2-methyl-6-nitro-2-[4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (0.192 g, yield 23%) as a light yellow solid.

¹H-NMR (CDCl₃) δppm:

1.68 (3H, s), 2.46 - 3.39 (8H, m), 3.95 (1H, d, J = 10.2 Hz), 4.49 (1H, br), 5.98 (1H, s), 7.16 (2H, d, J = 8.3 Hz), 7.35 (2H, d, J = 8.3 Hz), 7.53 (1H, s).

Example 253

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]propan-2-ol

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (500 mg, 2.30 mmol) and 4-(4-trifluoromethylphenoxy)piperidine (730 mg, 3.0 mmol) in DMF (10 ml) were stirred at 70-75°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water, and extracted with ethyl acetate. The extract was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]propan-2-ol (1.06 g, yield 99%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.14 (3H, s), 1.80 - 2.04 (4H, m), 2.38 (1H, d, J = 14.0 Hz), 2.48 - 2.68 (2H, m), 2.52 (1H, d, J = 14.0 Hz), 2.77 - 2.95 (2H, m), 3.73 (1H, s), 4.01 (2H, s), 4.39 - 4.46 (1H, m), 6.93 - 6.97 (2H, m), 7.49 - 7.55 (2H, m), 8.08 (1H, s).

Example 254

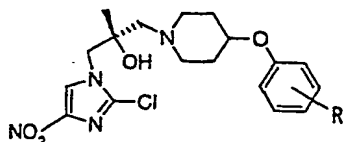
Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylbenzyloxy)piperidin-1-yl]propan-2-ol

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-

nitroimidazole prepared in Example 12 (700 mg, 3.22 mmol) and 4-(4-trifluoromethylbenzyloxy)piperidine (1.09 g, 4.86 mol) in DMF (10 ml) were stirred at 70-75°C for 4 hours. The reaction mixture was allowed to
5 return to room temperature, poured into water and extracted with ethyl acetate. The extract was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue
10 was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylbenzyloxy)piperidin-1-yl]propan-2-ol (1.36 g, yield 87%) as a yellow oil.
15 ¹H-NMR (CDCl₃) δppm:
1.12 (3H, s), 1.61 - 1.78 (2H, m), 1.88 - 1.96 (2H, m), 2.32 (1H, d, J = 13.9 Hz), 2.35 - 2.56 (2H, m), 2.47 (1H, d, J = 13.9 Hz), 2.72 - 2.81 (1H, m), 2.86 - 2.95 (1H, m), 3.44 - 3.51 (1H, m), 3.63 (1H, bs), 3.97 (2H,
20 s), 4.59 (2H, s), 7.43 - 7.47 (2H, m), 7.58 - 7.62 (2H, m), 8.05 (1H, s).

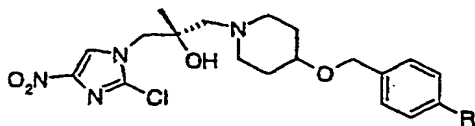
Using corresponding starting materials gave compounds of Examples 255 to 260 shown in the following table in the same manner as in Example 254.

Table 13



| Example | R | ¹ H NMR (CDCl ₃) δ | Yield (%) |
|---------|--------------------|---|-----------|
| 255 | 4-OCF ₃ | 1.13(3H, s), 1.77-1.89(2H, m), 1.91-2.01(2H, m), 2.37(1H, d, J=13.9Hz), 2.45-2.67(2H, m), 2.51(1H, d, J=13.9Hz), 2.75-2.95(2H, m), 3.71(1H, s), 4.00(2H, s), 4.17-4.34(1H, m), 6.85-6.91(2H, m), 7.11-7.15(2H, m), 8.07(1H, s). | 99 |
| 256 | 4-Cl | 1.13(3H, s), 1.73-1.88(2H, m), 1.91-2.02(2H, m), 2.36(1H, d, J=13.9Hz), 2.44-2.63(2H, m), 2.50(1H, d, J=13.9Hz), 2.76-2.95(2H, m), 3.64(1H, s), 3.99(2H, s), 4.26-4.35(1H, m), 6.79-6.86(2H, m), 7.18-7.26(2H, m), 8.06(1H, s). | 99 |
| 257 | 4-CN | 1.14(3H, s), 1.81-1.92(2H, m), 1.95-2.03(2H, m), 2.36(1H, d, J=13.9Hz), 2.47-2.68(2H, m), 2.51(1H, d, J=13.9Hz), 2.77-2.94(2H, m), 3.53(1H, s), 4.00(2H, s), 4.40-4.47(1H, m), 6.90-6.96(2H, m), 7.53-7.60(2H, m), 8.06(1H, s). | 99 |
| 258 | 3-CF ₃ | 1.14(3H, s), 1.81-1.91(2H, m), 1.94-2.02(2H, m), 2.37(1H, d, J=13.9Hz), 2.47-2.68(2H, m), 2.51(1H, d, J=13.9Hz), 2.77-2.97(2H, m), 3.61(1H, s), 3.99(2H, s), 4.38-4.44(1H, m), 7.04-7.12(2H, m), 7.18-7.22(1H, m), 7.35-7.42(1H, m), 8.07(1H, s). | 99 |

Table 14



| Example | R | ¹ H NMR (CDCl ₃) δ |
|---------|------------------|--|
| 259 | OCF ₃ | 1.12(3H, s), 1.66-1.76(2H, m), 1.86-1.95(2H, m), 2.32(1H, d, J=13.9Hz), 2.36-2.55(2H, m), 2.46(1H, d, J=13.9Hz), 2.72-2.82(1H, m), 2.85-2.96(1H, m), 3.42-3.49(1H, m), 3.69(1H, s), 4.00(2H, s), 4.52(2H, s), 7.17-7.21(2H, m), 7.35-7.39(2H, m), 8.06(1H, s). |
| 260 | Cl | 1.10(3H, s), 1.65-1.74(2H, m), 1.85-1.92(2H, m), 2.31(1H, d, J=13.9Hz), 2.38-2.54(2H, m), 2.46(1H, d, J=13.9Hz), 2.71-2.79(1H, m), 2.84-2.95(1H, m), 3.38-3.48(1H, m), 3.72(1H, s), 3.96(2H, s), 4.48(2H, s), 7.23-7.32(2H, m), 8.05(1H, s). |

Example 261

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(3-phenyl-2-propenyloxy)piperidin-1-yl]-propan-2-ol

5 Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 (0.198 g, 0.910 mmol) and 4-(3-phenyl-2-propenyloxy)piperidine (0.198 g, 0.910 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(3-phenyl-2-propenyloxy)piperidin-1-yl]propan-2-ol (0.192 g, yield 49%) as a brown oil in the same manner as in Example 254.

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 1.55 - 1.98 (4H, m), 2.28 - 2.94 (6H, m),
15 3.41 - 3.49 (1H, m), 3.62 (1H, br), 3.95 (2H, s), 4.16 (1H, d, J = 6.0 Hz), 4.17 (1H, d, J = 6.0 Hz), 6.28 (1H, ddd, J = 6.0 Hz, 6.0 Hz, 15.9 Hz), 6.60 (1H, d, J = 15.9 Hz), 7.21 - 7.42 (5H, m), 8.05 (1H, s).

Example 262

20 Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-{4-[3-(4-chlorophenyl)-2-propenyloxy]piperidin-1-yl}-2-methylpropan-2-ol

 Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 (0.217 g, 1.00 mmol) and 4-[3-(4-chloro-phenyl)-2-propenyloxy]piperidine (0.250 g, 0.995 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-{4-[3-(4-chlorophenyl)-2-propenyloxy]piperidin-1-yl}-2-

methylpropan-2-ol (0.263 g, yield 56%) as a brown liquid in the same manner as in Example 254.

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 1.55 - 2.01 (4H, m), 2.28 - 2.99 (6H, m),
5 3.40 - 3.51 (1H, m), 3.60 (1H, br), 3.96 (2H, s), 4.13
- 4.16 (2H, m), 6.20 - 6.31 (1H, m), 6.56 (1H, d, J =
15.7 Hz), 7.19 - 7.34 (4H, m), 8.05 (1H, s).

Example 263

Preparation of (S)-2-{4-[3-(4-chlorophenyl)propoxy]-
10 piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-
nitroimidazole prepared in Example 12 (0.103 g, 0.473
mmol) and 4-[3-(4-chlorophenyl)propoxy]piperidine
15 (0.109 g, 0.430 mmol) were dissolved in DMF (10 ml),
and the solution was stirred at 60°C for 4 hours. The
reaction mixture was added water and extracted with
ethyl acetate. The organic phase was combined, washed
with water and a saturated saline solution, dried over
20 sodium sulfate and then filtered. The resulting
filtrate was concentrated under reduced pressure. The
residue was purified by silica gel column
chromatography (n-hexane/ethyl acetate = 2/3) to afford
an oil. The oil was dissolved in DMF (2 ml). To the
25 solution, sodium hydride (15 mg, 0.375 mmol) was added
with cooling on ice-bath followed by stirring at room
temperature for 3 hours. To the reaction mixture,
water was added, and the precipitates were filtered

off, purified by silica gel column chromatography (methylene chloride/ethyl acetate = 6/1) and then recrystallized from ethyl acetate/n-hexane = 1/3 (6 ml) to afford (S)-2-{4-[3-(4-chlorophenyl)propoxy]-

5 piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (36 mg, yield 19%) as a white powder.

Melting point 88.8-91.9°C.

Example 264

10 Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-{4-[2-(4-chlorophenyl)ethoxy]piperidin-1-yl}-2-methylpropan-2-ol

Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 (0.076 g, 0.350 mmol) and 4-[2-(4-chlorophenyl)ethoxy]-
15 piperidine (0.080 g, 0.334 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-{4-[2-(4-chlorophenyl)ethoxy]-piperidin-1-yl}-2-methylpropan-2-ol (0.109 g, yield 71%) as a light yellow oil in the same manner as in

20 Example 254.

¹H-NMR (CDCl₃) δppm:

1.10 (3H, s), 1.51 - 1.72 (2H, m), 1.78 - 1.92 (2H, m),
2.24 - 2.50 (4H, m), 2.55 - 2.88 (4H, m), 3.29 - 3.39
(1H, m), 3.58 - 3.66 (3H, m), 3.94 (2H, s), 7.15 (2H,
25 d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz), 8.04 (1H, s).

Example 265

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[2-(4-trifluoromethylphenyl)ethoxy]-

piperidin-1-yl}propan-2-ol

Triphenyl-(4-trifluoromethylbenzyl)-
phosphonium bromide (3.00 g, 5.98 mmol) was dissolved
in DMSO (50 ml). To the solution, sodium hydride
5 (0.239 g, 5.98 mmol) was added with cooling on ice-bath
followed by stirring at room temperature for 1 hour.
To the solution, a solution of benzyl 4-
formyloxypiperidine-1-carboxylate (1.497 g, 5.69 mmol)
in DMSO (10 ml) was added dropwise followed by stirring
10 at 60°C for 7 hours. The reaction mixture was added
water and extracted with ethyl acetate twice. The
organic phases were combined, washed with water and a
saturated saline solution, dried over sodium sulfate
and then filtered. The filtrate was concentrated under
15 reduced pressure. The residue was purified by silica
gel column chromatography (n-hexane/ethyl acetate =
4/1) and then purified by silica gel column
chromatography (methylene chloride/ethyl acetate = 9/1)
to afford benzyl 4-[2-(4-trifluoromethylphenyl)-
20 vinyloxy]piperidin-1-carboxylate as a colorless oil.

The resulting benzyl 4-[2-(4-trifluoromethyl-
phenyl)vinyloxy]piperidin-1-carboxylate was dissolved
in ethanol (10 ml) and reduced by catalytic
hydrogenation over 10%Pd/C (90 mg) at room temperature
25 under atmospheric pressure. The reaction mixture was
filtered through Celite. The filtrate was concentrated
under reduced pressure to afford 4-[2-(trifluoromethyl-
phenyl)ethoxy]piperidine as a brown liquid.

Using the resulting 4-[2-(trifluoromethyl-phenyl)ethoxy]piperidine and (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.184 g, 0.844 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-[2-(4-trifluoromethylphenyl)ethoxy]piperidin-1-yl]propan-2-ol (0.088 g, yield 3%) as a brown oil in the same manner as in Example 254.

¹H-NMR (CDCl₃) δppm:

1.10 (3H, s), 1.49 - 1.92 (4H, m), 2.24 - 2.81 (6H, m), 2.92 (2H, t, J = 6.8 Hz), 3.30 - 3.35 (1H, m), 3.65 (2H, t, J = 6.8 Hz), 3.94 (2H, s), 7.34 (2H, d, J = 8.2 Hz), 7.54 (2H, d, J = 8.2 Hz), 8.04 (1H, s).

Example 266

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol

Using (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 and N-(piperidin-4-yl)-4-trifluoromethoxyaniline gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol (1.36 g, yield 88%) as a yellow oil in the same manner as in Example 254.

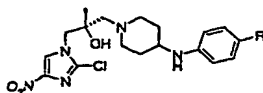
¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 1.41 - 1.57 (2H, m), 2.03 - 2.08 (2H, m), 2.34 (1H, d, J = 13.9 Hz), 2.49 - 2.59 (3H, m), 2.65 - 2.77 (2H, m), 3.08 - 3.16 (2H, m), 3.24 - 3.41 (1H, m),

3.97 (2H, s), 6.47 - 6.55 (2H, m), 6.98 - 7.04 (2H, m),
8.05 (1H, s).

Using corresponding starting materials gave
compounds of Examples 267 to 269 shown in the following
5 table in the same manner as in Example 266.

Table 15



| Example | R | Yield (%) | ¹ H NMR (CDCl ₃) δ |
|---------|-----------------|-----------|---|
| 267 | Cl | 99 | 1.13(3H, s), 1.40-1.53(2H, m), 2.00-2.06(2H, m), 2.35(1H, d, J=13.9Hz), 2.45-2.59(3H, m), 2.71-3.01(2H, m), 3.18(1H, br), 3.48-3.58(2H, m), 3.97(2H, s), 6.47-6.54(2H, m), 7.07-7.14(2H, m), 8.05(1H, s). |
| 268 | CF ₃ | 99 | 1.14(3H, s), 1.42-1.59(2H, m), 2.03-2.08(2H, m), 2.35(1H, d, J=13.9Hz), 2.49-2.60(2H, m), 2.50(1H, d, J=13.9Hz), 2.74-2.98(2H, m), 3.31-3.39(1H, m), 3.51(1H, s), 3.87(1H, d, J=9.3Hz), 3.97(2H, s), 6.58(2H, d, J=8.7Hz), 7.39(2H, d, J=8.7Hz), 8.05(1H, s). |
| 269 | CN | 99 | 1.13(3H, s), 1.40-1.53(2H, m), 2.00-2.06(2H, m), 2.35(1H, d, J=13.9Hz), 2.45-2.59(2H, m), 2.49(1H, d, J=13.9Hz), 2.71-3.01(2H, m), 3.18(1H, br), 3.48-3.58(2H, m), 3.97(2H, s), 6.51-6.57(2H, m), 7.38-7.44(2H, m), 8.05(1H, s). |

Example 270

20 Preparation of (S)-1-(4-piperidinopiperidin-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-propan-2-ol

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.500 g, 2.29 mmol) and 4-piperidinopiperidine (0.425 g, 2.53 mmol)
25 were dissolved in DMF (5 ml), and the solution was stirred at 70°C for 5 hours. The reaction mixture was added water and extracted with ethyl acetate twice. The organic phases were combined, washed with water and

a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-
 5 hexane/ethyl acetate = 3/2) using basic silica gel to afford (S)-1-(4-piperidinopiperidin-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-propan-2-ol (0.656 g, yield 74%) as a brown oil.

¹H-NMR (CDCl₃) δppm:

10 1.11 (3H, s), 1.38 - 1.89 (10H, m), 2.18 - 2.55 (9H, m), 2.70 - 2.81 (1H, m), 2.89 - 3.01 (1H, m), 3.67 (1H, br), 3.94 (1H, s), 8.05 (1H, s).

Example 271

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-
 15 methyl-3-{[4-(4-trifluoromethoxyphenyl)sulfanyl]-piperidin-1-yl}propan-2-ol

Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 and 4-[4-(trifluoromethoxy)phenylsulfanyl]piperidine gave
 20 (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{[4-(4-trifluoromethoxyphenyl)sulfanyl]piperidin-1-yl}propan-2-ol (3.4 g, yield 99%) as a yellow oil in the same manner as in Example 270.

¹H-NMR (CDCl₃) δppm:

25 1.11 (3H, s), 1.58 - 1.73 (2H, m), 1.91 - 1.99 (2H, m), 2.32 (1H, d, J = 13.9 Hz), 2.41 - 2.50 (2H, m), 2.46 (1H, d, J = 13.9 Hz), 2.75 - 3.09 (4H, m), 3.97 (2H, s), 7.11 - 7.17 (2H, m), 7.36 - 7.53 (2H, m), 8.04 (1H,

s).

Example 272

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]propan-2-ol

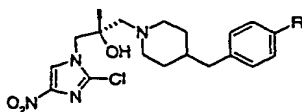
Using 4-(4-trifluoromethoxybenzyl)piperidine and (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]propan-2-ol (crude) as a yellow oil in the same manner as in Example 270.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.10 (3H, m), 1.22 - 1.71 (5H, m), 2.26 - 2.55 (6H, m), 2.66 - 2.96 (3H, m), 3.94 (2H, s), 7.09 - 7.18 (4H, m), 8.06 (1H, s).

Using corresponding starting materials gave compounds of Examples 273 and 274 shown in the following table in the same manner as in Example 272.

Table 16



| Example | R | Yield (%) | $^1\text{H NMR}$ (CDCl_3) δ |
|---------|------------------|-----------|--|
| 273 | 4- CF_3 | 56 | 1.10(3H, s), 1.14-1.38(2H, m), 1.47-1.64(3H, m), 2.29(1H, d, $J=13.9\text{Hz}$), 2.30-2.40(2H, m), 2.43(1H, d, $J=13.9\text{Hz}$), 2.60(2H, d, $J=6.5\text{Hz}$), 2.69(1H, d, $J=11.7\text{Hz}$), 2.90(1H, d, $J=11.7\text{Hz}$), 3.74(1H, br), 3.94(2H, s), 7.22-7.26(2H, m), 7.52-7.54(2H, m), 8.05(1H, s). |
| 274 | 4-Cl | 65 | 1.10(3H, s), 1.14-1.63(5H, m), 2.26-2.52(7H, m), 2.68(1H, d, $J=11.5\text{Hz}$), 2.90(1H, d, $J=11.5\text{Hz}$), 3.94(2H, s), 7.00-7.08(2H, m), 7.20-7.29(2H, m), 8.05(1H, s). |

Example 275

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)propan-2-ol

- 5 4-Phenyl-1,2,3,6-tetrahydropyridine hydrochloride (0.495 g, 2.53 mmol) was added to a sodium hydroxide solution, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The
- 10 filtrate was concentrated under reduced pressure. To the residue, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.5 g, 2.29 mmol) and DMF (5 ml) were added followed by stirring at 70°C for 5 hours. The reaction mixture was
- 15 poured into water and extracted with ethyl acetate twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and
- 20 the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)propan-2-ol (0.492 g, yield 57%) as a yellow oil.
- 25 ¹H-NMR (CDCl₃) δppm:
- 1.17 (3H, s), 2.47 (1H, d, J = 13.9 Hz), 2.58 - 2.64 (3H, m), 2.78 - 3.00 (2H, m), 3.27 - 3.40 (2H, m), 3.62 (1H, br), 4.01 (2H, s), 6.02 - 6.05 (1H, m), 7.23 -

7.41 (5H, m), 8.07 (1H, s).

Example 276

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(4-phenylpiperidin-1-yl)propan-2-ol

- 5 4-Phenylpiperidine hydrochloride (0.522 g, 2.64 mmol) was added to a sodium hydroxide solution, and extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure.
- 10 To the residue, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.5 g, 2.29 mmol) and DMF (5 ml) were added followed by stirring at 70°C for 5 hours. The reaction mixture was poured into water and extracted with ethyl acetate
- 15 twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column
- 20 chromatography (n-hexane/ethyl acetate = 2/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(4-phenylpiperidin-1-yl)propan-2-ol (0.703 g, yield 81%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

- 25 1.14 (3H, s), 1.76 - 1.89 (4H, m), 2.36 (1H, d, J = 13.9 Hz), 2.48 - 2.61 (4H, m), 2.75 - 2.89 (1H, m), 2.98 - 3.09 (1H, m), 3.75 (1H, br), 3.98 (2H, s), 7.18 - 7.35 (5H, m), 8.08 (1H, s).

Example 277

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenyl)piperidin-1-yl]propan-2-ol

5 (R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.329 g, 1.51 mmol) and 4-(4-trifluoromethylphenyl)piperidine (0.40 g, 1.66 mmol) were dissolved in DMF (5 ml) followed by stirring at 70°C for 3 hours. The reaction mixture was
 10 poured into water and extracted with ethyl acetate twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The
 15 residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenyl)piperidin-1-yl]propan-2-ol (0.361 g, yield 54%) as a brown oil.

20 ¹H-NMR (CDCl₃) δppm:

1.13 (3H, s) 1.71 - 1.93 (4H, m), 2.36 (1H, d, J = 14.0 Hz), 2.48 - 2.65 (4H, m), 2.77 - 2.90 (1H, m), 3.01 - 3.14 (1H, m), 3.64 (1H, br), 3.99 (2H, s), 7.32 (2H, d, J = 8.1 Hz), 7.57 (2H, d, J = 8.1 Hz), 8.07 (1H, s).

25 Example 278

Preparation of tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperidin-4-yl}carbamate

Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 and tert-butyl piperidin-4-ylcarbamate gave tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperidin-4-yl}carbamate (yield 92%) a yellow oil in the same manner as in Example 277.

¹H-NMR (CDCl₃) δppm:

1.11 (3H, s), 1.32 - 1.51 (2H, m), 1.44 (9H, m), 1.90 - 1.96 (2H, m), 2.32 (1H, d, J = 13.9 Hz), 2.39 - 2.55 (2H, m), 2.46 (1H, d, J = 13.9 Hz), 2.67 - 2.96 (3H, m), 3.44 (1H, br), 3.59 (1H, s), 3.96 (2H, s), 8.05 (1H, s).

Example 279

Preparation of tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methyl-propyl]piperidin-4-yl}-N-[2-(4-trifluoromethylphenyl)-ethyl]carbamate

Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 (0.332 g, 0.891 mmol) and tert-butyl piperidin-4-yl-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate (0.194 g, 0.891 mmol) gave tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methyl-propyl]piperidin-4-yl}-N-[2-(4-trifluoromethylphenyl)-ethyl]carbamate (0.370 g, yield 70%) as a light yellow oil in the same manner as in Example 277.

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 1.49 (9H, s), 1.55 - 1.80 (4H, m), 2.17 -

2.57 (4H, m), 2.70 - 2.98 (4H, m), 3.21 - 3.30 (2H, m),
 3.50 (1H, s), 3.95 (2H, s), 7.31 (2H, d, $J = 8.2$ Hz),
 7.57 (2H, d, $J = 8.2$ Hz), 8.05 (1H, s).

Example 280

- 5 Preparation of (S)-2-methyl-6-nitro-2-[4-(4-trifluoro-
 methylphenoxy)piperidin-1-ylmethyl]-2,3-dihydroimidazo-
 [2,1-b]oxazole

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-
 methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-
 10 yl]propan-2-ol prepared in Example 253 (1.06 g, 2.3
 mmol) was dissolved in DMF (15 ml). To the solution,
 sodium hydride (110 mg, 2.76 mmol) was added with
 cooling on ice-bath followed by stirring at room
 temperature overnight. The reaction mixture was poured
 15 into water and extracted with ethyl acetate. The
 organic phase was washed with a saturated saline
 solution, dried over magnesium sulfate and then
 filtered. The filtrate was concentrated under reduced
 pressure. The residue was purified by silica gel
 20 column chromatography (methylene chloride/ethyl acetate
 = 5/1) and crystallized from methylene chloride-
 diisopropyl ether to afford (S)-2-methyl-6-nitro-2-[4-
 (4-trifluoromethylphenoxy)piperidin-1-ylmethyl]-2,3-
 dihydroimidazo[2,1-b]oxazole (431 mg, yield 44%) as a
 25 white powder.

MS 427(M+1)⁺

Optical purity 97.8% e.e.

$[\alpha]_D^{27} = -2.07^\circ$ (concentration: 1.064, CHCl₃)

¹H-NMR (CDCl₃) δppm:

1.61 (3H, s), 1.67 - 1.92 (4H, m), 2.41 - 2.51 (1H, m),
2.57 (1H, d, J = 14.9 Hz), 2.58 - 2.67 (1H, m), 2.88
(1H, d, J = 14.9 Hz), 2.74 - 2.98 (2H, m), 3.91 (1H, d,
5 J = 9.7 Hz), 4.31 (1H, d, J = 9.7 Hz), 4.28 - 4.36 (1H,
m), 6.91 (2H, d, J = 8.7 Hz), 7.51 (2H, d, J = 8.7 Hz),
7.54 (1H, s).

Example 281

10 Preparation of (S)-2-methyl-6-nitro-2-[4-(4-trifluoro-
methylbenzyloxy)piperidin-1-ylmethyl]-2,3-
dihydroimidazo[2,1-b]oxazole

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-
methyl-3-[4-(4-trifluoromethylbenzyloxy)piperidin-1-
15 yl]propan-2-ol prepared in Example 254 (1.36 g, 2.8
mmol) was dissolved in DMF (15 ml). To the solution,
sodium hydride (134 mg, 3.36 mmol) was added with
cooling on ice-bath followed by stirring at room
temperature overnight. The reaction mixture was poured
20 into water and extracted with ethyl acetate. The
organic phase was washed with a saturated saline
solution, dried over magnesium sulfate and then
filtered. The filtrate was concentrated under reduced
pressure, and the residue was purified by silica gel
25 column chromatography (methylene chloride/ethyl acetate
= 10/1) and crystallized from methylene chloride-
diisopropyl ether to afford (S)-2-methyl-6-nitro-2-[4-
(4-trifluoromethylbenzyloxy)piperidin-1-ylmethyl]-2,3-

dihydroimidazo[2,1-b]oxazole (431 mg, yield 44%) as a white powder.

MS 440(M-1)⁺

Melting point 91-92°C

5 Optical purity 99.6% e.e.

$[\alpha]_D^{27} = -8.63^\circ$ (concentration: 1.066, CHCl₃)

¹H-NMR (CDCl₃) δppm:

1.44 - 1.66 (2H, m), 1.60 (3H, s), 1.71 - 1.85 (2H, m),
2.28 - 2.38 (1H, m), 2.44 - 2.56 (1H, m), 2.52 (1H, d,
10 J = 14.9 Hz), 2.72 - 2.81 (1H, m), 2.84 (1H, d, J =
14.9 Hz), 2.87 - 2.94 (1H, m), 3.33 - 3.41 (1H, m),
3.88 (1H, d, J = 9.6 Hz), 4.31 (1H, d, J = 9.6 Hz),
4.54 (2H, s), 7.41 - 7.44 (2H, m), 7.52 (1H, s), 7.56 -
7.60 (2H, m).

15 Example 282

Preparation of (S)-2-[4-(4-trifluoromethoxyphenyl)aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Using (S)-1-(2-chloro-4-nitroimidazol-1-yl)-
20 2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol prepared in Example 266 gave (S)-2-[4-(4-trifluoromethoxyphenyl)aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (yield 73%) as a white powder in the same manner as in Example
25 281.

Melting point 107.5-109.0°C

MS 441(M⁺)

Optical purity 99.8% e.e.

$[\alpha]_D^{27} = 19.19^\circ$ (concentration: 1.006, CHCl_3).

Example 283

Preparation of tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Using tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperidin-4-yl}carbamate prepared in Example 278 gave tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate (yield 49%) as a white powder in the same manner as in Example 281.

MS 381(M^+)

Melting point $158.5\text{--}160.7^\circ\text{C}$.

Example 284

Preparation of tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate

Using tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methyl-propyl]piperidin-4-yl}-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate prepared in Example 279 (0.37 g, 0.627 mmol) gave tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate (0.211 g, yield 63%) as a light yellow powder in the same manner as in Example 281.

Melting point $206.8\text{--}208.6^\circ\text{C}$.

Example 285

Preparation of (S)-2-methyl-6-nitro-2-{4-[4-(trifluoromethoxyphenyl)sulfanyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

- 5 Using (S)-1-(2-chloro-4-nitro-imidazol-1-yl)-2-methyl-3-{[4-(4-trifluoromethoxyphenyl)sulfanyl]piperidin-1-yl}propan-2-ol prepared in Example 271 gave (S)-2-methyl-6-nitro-2-{4-[4-(trifluoromethoxyphenyl)sulfanyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole (yield 62%) as a white powder in the same manner as in Example 281.

MS 458 (M⁺)

Melting point 133.0-137.4°C.

Example 286

- 15 Preparation of (S)-2-methyl-6-nitro-2-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole

- Using (S)-1-(2-chloro-4-nitro-imidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]propan-2-ol prepared in Example 272 gave (S)-2-methyl-6-nitro-2-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole (yield 55%) as a white powder in the same manner as in Example 281.

- 25 Melting point 111.0-112.5°C

MS: 440 (M⁺)

Optical purity 99.0% e.e.

$[\alpha]_D^{27} = 5.38^\circ$ (concentration: 1.004, CHCl₃).

Example 287

Preparation of (S)-2-methyl-6-nitro-2-(4-phenyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole

5 (S)-1-(2-Chloro-4-nitro-imidazol-1-yl)-2-methyl-3-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)propan-2-ol prepared in Example 275 (0.492 g, 1.31 mmol) was dissolved in DMF (8 ml). To the solution, sodium hydride (63 mg, 1.57 mmol) was added with
10 cooling on ice-bath followed by stirring at room temperature for 3 hours. To the reaction mixture, water was added. After extraction with ethyl acetate, the organic phase was washed with water and a saturated saline solution, dried over sodium sulfate and then
15 filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 4/1) and recrystallized from methylene chloride-ethyl acetate to afford (S)-2-methyl-6-nitro-2-(4-phenyl-
20 1,2,3,6-tetrahydropyridin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole (0.059 g, yield 13%) as a light yellow solid.

Melting point 200.1-201°C.

Example 288

25 Preparation of (S)-2-methyl-6-nitro-2-(4-phenylpiperidin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole

(S)-1-(2-Chloro-4-nitro-imidazol-1-yl)-2-methyl-3-(4-phenylpiperidin-1-yl)propan-2-ol prepared

in Example 276 (0.703 g, 1.86 mmol) was dissolved in DMF (5 ml). To the solution, sodium hydride (89 mg, 2.23 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 3 hours. To the
5 reaction mixture, water was added. The precipitates were filtered off, purified by silica gel column chromatography (n-hexane/acetone = 3/1) and recrystallized from ethyl acetate to afford (S)-2-methyl-6-nitro-2-(4-phenylpiperidin-1-ylmethyl)-2,3-
10 dihydroimidazo[2,1-b]oxazole (0.230 g, yield 36%) as a white powder.
Melting point 158.8-163.9°C.

Using corresponding starting materials gave compounds of Examples 289 to 294 in the same manner as
15 in Example 288.

Example 289

(S)-1'-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-[1,4']bipiperidinyl
Melting point 163.4-164.9°C.

20 Example 290

(S)-2-Methyl-6-nitro-2-[4-(4-trifluoromethylphenyl)-piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 138.7-139.9°C.

Example 291

25 (S)-2-Methyl-6-nitro-2-[4-(3-phenyl-2-propenyloxy)-piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 91.3-92.7°C.

Example 292

(S)-2-{4-[3-(4-Chlorophenyl)-2-propenyloxy]piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 140.6-142.8°C.

5 Example 293

(S)-2-Methyl-6-nitro-2-{4-[2-(4-trifluoromethylphenyl)ethoxy]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 84.6-86.8°C.

10

 Example 294

(S)-2-{4-[2-(4-Chlorophenyl)ethoxy]piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

15 Melting point 92.5-94°C.

 Example 295

Preparation of (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-methyl-4-trifluoromethoxyaniline

20 (S)-2-[4-(4-Trifluoromethoxyphenyl)amino-piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 282 (400 mg, 0.90 mmol) was dissolved in methanol (10 ml). To the solution, a 37% formaldehyde solution (0.13 ml, 4.52 mmol), sodium cyanotrihydroborate (170 mg, 2.71 mmol) and acetic acid (0.17 ml, 2.71 mmol) were added followed by stirring at room temperature for 30 minutes. The reaction mixture was poured into a

saturated sodium hydrogencarbonate solution and extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and recrystallized from methylene chloride-diisopropyl ether to afford (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-methyl-4-trifluoromethoxyaniline (309 mg, yield 78%) as a light yellow crystals.

Optical purity 99.9% e.e.

$[\alpha]_d^{17} = 7.77$ (concentration: 1.042, CHCl_3)

MS 455 (M^+)

Melting point 133.2-134.4°C.

Example 296

Preparation of (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-(4-trifluoromethoxyphenyl)acetamide

(S)-2-[4-(4-Trifluoromethoxyphenyl)amino-piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 282 (153 mg, 0.35 mmol) was dissolved in methylene chloride (5 ml). To the solution, triethylamine (30 μl) and acetyl chloride (30 μl) were added followed by stirring at room temperature for 1.5 hours. The reaction mixture was poured into water and extracted with methylene chloride. The organic phase was dried over

magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-(4-trifluoromethoxyphenyl)acetamide (82 mg, yield 49%) as a white powder.

10 MS 484(M+1)⁺

Melting point 137.0-138.7°C.

Example 297

Preparation of (S)-2-{4-N-[(4-trifluoromethylphenyl)-acetyl]aminopiperidin-1-yl}methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

15 Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (0.1 g, 0.262 mmol) was dissolved in ethanol (4 ml). To the solution, 6 N hydrochloric acid (3 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene (4 ml) chloride and triethylamine (4 ml) were added. The resulting mixture was stirred at room temperature for 5 minutes and then concentrated. To the residue, toluene (10 ml) was added. The solution was concentrated to remove water azeotropically. To the residue, 4-

trifluoromethylphenylacetic acid (0.064 g, 0.315 mmol), methylene chloride (4 ml), triethylamine (0.06 ml, 0.393 mmol) and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (WSCD) (0.065 g, 0.341 mmol) were added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the mixture was extracted with methylene chloride twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 3/2) and recrystallized from ethyl acetate (3 ml) to afford (S)-2-{4-N-[(4-trifluoromethylphenyl)acetyl]aminopiperidin-1-yl}methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (32 mg, yield 26%) as a white powder. Melting point 152.7-154.3°C.

Example 298

Preparation of 4-trifluoromethylbenzyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (0.300 g, 0.787 mmol) was dissolved in methylene chloride (4 ml). To the solution, trifluoroacetic acid (2 ml) was added followed by stirring at room temperature for 2 hours.

The reaction mixture was concentrated under reduced pressure, and added methylene chloride (4 ml) and triethylamine (4 ml). The mixture was stirred at room temperature for 5 minutes and concentrated under reduced pressure. The residue was dissolved in DMF (6 ml). To the solution, a mixture of 4-(trifluoromethyl)benzyl alcohol (0.166 g, 0.944 mmol) in DMF (4 ml) and 1,1'-carbonyldiimidazole (0.153 g, 0.944 mmol) stirred at room temperature for 4 hours was added followed by stirring at room temperature overnight and then at 65°C for 8 hours. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/acetone = 2/1) and recrystallized from ethyl acetate to afford 4-trifluoromethylbenzyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate (0.107 g, yield 28%) as a light yellow powder.

Melting point 141.2-144°C.

Using corresponding starting materials gave compounds of Examples 299 and 300 in the same manner as in Example 298.

Example 299

1-(4-Trifluoromethylphenyl)piperidin-4-yl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Melting point 134.4-136.9°C.

5 Example 300

4-Trifluoromethoxybenzyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Melting point 156.2-158.5°C.

10 Example 301

Preparation of (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-4-trifluoromethylbenzylamine

15 Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (0.300 g, 0.787 mmol) was dissolved in methylene chloride (4 ml). To the solution, trifluoroacetic acid (2 ml) was added followed by stirring at room temperature for 1 hour.

20 The reaction mixture was concentrated under reduced pressure and added methylene chloride (4 ml) and triethylamine (4 ml). The mixture was stirred at room temperature for 20 minutes and then concentrated under reduced pressure. The residue was dissolved in

25 methanol (5 ml). To the solution, 4-trifluoromethylbenzaldehyde (0.164 g, 0.945 mmol), sodium cyanotrihydroborate (0.099 g, 1.57 mmol) and acetic acid (0.09 ml, 1.57 mmol) were added followed by

stirring at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phases
5 were combined, washed with a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =
10 20/1) and recrystallized from isopropyl alcohol to afford (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-4-trifluoromethylbenzylamine (0.078 g, yield 22%) as a light yellow powder.
15 Melting point 148.6-152.9°C.

Example 302

Preparation of (S)-1-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-3-(4-trifluoromethylphenyl)urea

20 Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (0.300 g, 0.787 mmol) was dissolved in methylene chloride (4 ml). To the solution, trifluoroacetic acid (2 ml) was added
25 followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (4 ml) and triethylamine (4 ml). The mixture was stirred at room

temperature for 5 minutes and concentrated under reduced pressure. The residue was called "residue 1".

On the other hand, 4-(trifluoromethyl)aniline (0.139 g, 0.865 mmol) and pyridine (0.07 ml, 0.865 mmol) was dissolved in THF (4 ml). To the solution, Phenyl chloroformate (0.108 ml, 0.865 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was added water and extracted with ethyl acetate. The organic phase was washed with water, 10% hydrochloric acid and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure.

The resulting residue was dissolved in dimethylsulfoxide (6 ml). To the solution, the "residue 1" was added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water, a saturated sodium hydrogencarbonate solution and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (n-hexane/acetone = 2/1) and recrystallized from isopropyl alcohol-n-hexane (1:1) (6 ml) to afford (S)-1-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-3-(4-

trifluoromethylphenyl)urea (0.064 g, yield 17%) as a light yellow powder.

Melting point 136.8-139.9°C.

Example 303

- 5 Preparation of (S)-2-[4-N-(4-trifluoromethylbenzoyl)-aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (360 mg, 0.92 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (10 ml) and triethylamine (2 ml). To the solution, 4-trifluoromethylbenzoyl chloride (0.3 ml, 1.85 mmol) was added followed by stirring at room temperature for 1 hour. The reaction mixture was poured into water and extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) and crystallized from ethyl acetate-diisopropyl ether to afford (S)-2-[4-N-(4-trifluoro-

10

15

20

25

methylbenzoyl)aminopiperidin-1-yl]methyl-2-methyl-6-

nitro-2,3-dihydroimidazo[2,1-b]oxazole (232 mg, yield 55%) as a white powder.

MS 454 (M+H)⁺

Melting point 170.5-171.7°C.

5 Example 304

Preparation of (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-2-(4-trifluoromethylphenyl)ethylamine

10 Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate prepared in Example 284 (0.196 g, 0.354 mmol) was dissolved in methylene chloride (2 ml). To the solution, trifluoroacetic acid (1 ml) was added followed by
15 stirring at room temperature for 4 hours. To the reaction mixture, a saturated sodium hydrogencarbonate solution was added, and the solution was extracted with methylene chloride twice. The organic phases were combined, dried over sodium sulfate and then filtered.
20 The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and treated with isopropyl ether to afford (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-2-(4-
25 trifluoromethylphenyl)ethylamine (0.020 g, yield 12%) as a light yellow powder.
Melting point 80.7-84.2°C.

Example 305

Preparation of (S)-2-methyl-6-nitro-2-{4-[4-(trifluoromethoxy)benzenesulfinyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

5 (S)-2-Methyl-6-nitro-2-{4-[4-(trifluoromethoxyphenyl)sulfanyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 285 (300 mg, 0.65 mmol) was dissolved in methylene chloride (5 ml). To the solution, m-chloroperbenzoic acid (169
10 mg, 0.69 mmol) was added followed by stirring at room temperature for 30 minutes. The reaction mixture was diluted with methylene chloride. The solution was washed with a sodium thiosulfate solution, a saturated sodium hydrogencarbonate solution and a saturated
15 saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) and crystallized from ethyl
20 acetate-isopropyl ether to afford (S)-2-methyl-6-nitro-2-{4-[4-(trifluoromethoxy)benzenesulfinyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole (219 mg, yield 71%) as a white powder.

MS 475(M+H)⁺

25 Melting point 107-109°C.

Example 306

Preparation of 2-(4-tert-butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazole

2-Chloro-4-nitro-1H-imidazole (3.19 g, 21.6 mmol) and tert-butyl 4-(2-methyloxiran-2-ylmethyl)-piperazine-1-carboxylate (5.53 g, 21.6 mmol) and sodium acetate (1.95 g, 23.8 mmol) were dissolved in 1-propanol (50 ml) followed by stirring under reflux for 48 hours. The reaction mixture was diluted with methylene chloride. The solution was washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and treated with methylene chloride-diisopropyl ether to afford 2-(4-tert-butoxy-carbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (1.85 g, yield 23%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.43 (9H, s), 1.62 (3H, s), 2.45 - 2.68 (5H, m), 2.87 (1H, d, J = 14.9 Hz), 3.30 (4H, br), 3.93 (1H, d, J = 9.7 Hz), 4.30 (1H, d, J = 9.7 Hz), 7.54 (1H, s).

Using corresponding starting materials gave the compound of Example 307 in the same manner as in Example 306.

Example 307

2-[4-(4-Cyanophenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 18%

¹H-NMR (CDCl₃) δppm:

1.67 (3H, s), 2.60 - 2.80 (3H, m), 2.80 - 3.00 (3H, m),
3.22 (4H, br), 3.97 (1H, d, J = 9.8 Hz), 4.35 - 4.50
(1H, m), 6.78 - 6.85 (2H, m), 7.46 - 7.51 (2H, m), 7.55
5 (1H, s).

Example 308

Preparation of 2-[4-(4-trifluoromethylphenyl)piperazin-
1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazole

10 To a solution of 2-chloro-4-nitro-1H-
imidazole (1.59 g, 10.8 mmol) and 1-(2-methyloxiran-2-
ylmethyl)-4-(4-trifluoromethylphenyl)piperazine (3.23
g, 10.8 mmol) in 1-propanol (20 ml), sodium
hydrogencarbonate (1.95 g, 23.8 mmol) was added
15 followed by stirring under reflux overnight. The
reaction mixture was concentrated under reduced
pressure. The residue was added water, and the
solution was extracted with methylene chloride. The
organic phase was dried over sodium sulfate and then
20 filtered. The filtrate was concentrated under reduced
pressure. The residue was purified by silica gel
column chromatography (methylene chloride/methanol =
100/1) and crystallized from methylene chloride-
isopropyl ether to afford 2-[4-(4-trifluoro-
25 methylphenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazole (1.34 g, yield 29%) as
a light yellow powder.

MS 411 (M⁺)

Melting point 159-160°C.

Also, the above purification by silica gel column chromatography gives an intermediate, 2-chloro-1-{3-[4-(4-trifluoromethylphenyl)piperazin-1-yl]-2-hydroxy-2-methyl}propyl-4-nitroimidazole (697 mg, yield 15%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.17 (3H, s), 2.32 - 2.91 (6H, s), 3.26 - 3.31 (4H, m), 4.03 (2H, s), 6.71 (1H, s), 6.89 - 6.93 (2H, m), 7.45 - 7.51 (2H, m), 8.06 (1H, s).

Using corresponding starting materials gave compounds of Examples 309 to 311 in the same manner as in Example 308.

Example 309

2-[4-(Biphenyl-4-yl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 32%, melting point 223-227.8°C.

Example 310

2-[4-(4-Chlorophenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 14%, melting point 196.6-197.3°C.

Example 311

2-[4-(4-Trifluoromethoxyphenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 18%

¹H-NMR (CDCl₃) δppm:

1.61 (3H, s), 2.61 (1H, d, J = 14.8 Hz), 2.65 - 2.73 (2H, m), 2.82 - 2.95 (2H, m), 2.93 (1H, d, J = 14.8

Hz), 2.99 - 3.09 (4H, m), 3.94 (1H, d, $J = 9.7$ Hz), 4.34 (1H, d, $J = 9.7$ Hz), 6.78 - 6.86 (2H, m), 7.06 - 7.11 (2H, m), 7.53 (1H, s).

Example 312

- 5 Preparation of 1-[3-(4-tert-butoxycarbonylpiperazin-1-yl)-2-hydroxy-2-methyl]propyl-2-chloro-4-nitroimidazole
- 2-Chloro-4-nitro-1H-imidazole (863 mg, 5.85 mmol) and tert-butyl 4-(2-methyloxiran-2-ylmethyl)-piperazine-1-carboxylate (1.5 g, 5.85 mmol) was
- 10 dissolved in 1-propanol (10 ml) followed by stirring under reflux for 6 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. The residue was purified by
- 15 silica gel column chromatography (methylene chloride/methanol = 100/1) to afford 1-[3-(4-tert-butoxycarbonylpiperazin-1-yl)-2-hydroxy-2-methyl]propyl-2-chloro-4-nitroimidazole (705 mg, yield 29.8%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

- 20 1.15 (3H, s), 1.45 (9H, s), 2.35 (1H, d, $J = 13.9$ Hz), 2.45 - 2.65 (5H, m), 3.25 (1H, s), 3.42 (4H, t, $J = 4.3$ Hz), 4.00 (2H, s), 8.05 (1H, s).

- Using 2-chloro-4-nitro-1H-imidazole and tert-butyl 4-(oxiran-2-ylmethyl)piperazine-1-carboxylate,
- 25 tert-butyl 4-[2-(2-methyloxiran-2-yl)ethyl]piperazine-1-carboxylate or benzyl 4-(2-methyloxiran-2-ylmethyl)-piperazine-1-carboxylate gave compounds of Examples 313 to 315 in the same manner as in Example 312.

Example 313

Tert-butyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate

Light yellow powder, yield 43%

5 ¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 2.16 - 2.50 (4H, m), 2.55 - 2.70 (2H, m),
3.40 - 3.51 (4H, m), 3.64 (1H, s), 3.91 - 4.09 (2H, m),
4.17 (1H, dd, J = 2.0 Hz, 13.5 Hz), 8.00 (1H, s).

Example 314

10 Tert-butyl 4-[4-(2-chloro-4-nitroimidazol-1-yl)-3-hydroxy-3-methylbutyl]piperazine-1-carboxylate

White powder, yield 17%

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 1.40 - 1.74 (11H, m), 2.23 - 2.58 (5H,
15 m), 2.81 - 2.95 (1H, m), 3.26 - 3.51 (4H, m), 3.91 (1H,
d, J = 14.0 Hz), 3.99 (1H, d, J = 14.0 Hz), 6.94 (1H,
s), 8.07 (1H, s).

Example 315

20 Benzyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate

Light yellow oil, yield 81%

¹H-NMR (CDCl₃) δppm:

1.14 (3H, s), 2.35 - 2.76 (6H, m), 3.43 - 3.61 (4H, m),
4.01 (2H, s), 5.13 (2H, s), 7.28 - 7.43 (5H, m), 8.04
25 (1H, s).

Example 316

Preparation of isobutyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate

A mixture of 1-[3-(4-tert-butoxycarbonyl-piperazin-1-yl)-2-hydroxy-2-methyl]propyl-2-chloro-4-nitroimidazole prepared in Example 312 (150 mg, 0.37 mmol) and trifluoroacetic acid (5 ml) was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml). To the solution, triethylamine (0.23 ml, 1.63 mmol) and isobutyl chloroformate (112 mg, 0.82 mmol) were added in this order followed by stirring at room temperature for 30 minutes. The reaction mixture was washed with water, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure to afford isobutyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate, which was used in the next step without purification.

¹H-NMR (CDCl₃) δppm:

0.93 (6H, d, J = 6.7 Hz), 1.14 (3H, s), 1.82 - 2.00 (1H, m), 2.39 (1H, d, J = 13.9 Hz), 2.47 - 2.73 (5H, m), 3.11 (1H, d, J = 7.3 Hz), 3.17 (1H, d, J = 7.3 Hz), 3.41 - 3.55 (4H, m), 3.87 (2H, s), 4.04 (1H, s), 8.10 (1H, s).

Example 317

Preparation of benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

To a mixture of benzyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate prepared in Example 315 (55.22 g, 126.11 mmol) and 1,4-dioxane (550 ml), sodium
5 hydride (6.05 g, 151.25 mmol) was added followed by stirring under reflux for 14 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with
10 methylene chloride twice. The organic phases were washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl
15 acetate) to afford benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (26.54 g, yield 52%) as a white powder. Melting point 130.5-132.1°C

¹H-NMR (CDCl₃) δppm:

20 1.61 (3H, s), 2.38 - 2.69 (5H, m), 2.86 (1H, d, J = 14.8 Hz), 3.10 - 3.50 (4H, m), 3.92 (1H, d, J = 9.9 Hz), 4.33 (1H, d, J = 9.9 Hz), 5.11 (2H, s), 7.23 - 7.38 (5H, m), 7.53 (1H, s).

Using corresponding starting materials gave
25 compounds of Examples 318 to 320 in the same manner as in Example 317.

Example 318

Isobutyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Light yellow powder, yield 39%, melting point 176.5-177.3°C.

Example 319

- 5 Tert-butyl 4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

White powder, yield 45%.

Melting point 185-188°C (decomposition)

¹H-NMR (CDCl₃) δppm:

- 10 1.45 (9H, s), 2.48 - 2.58 (4H, m), 2.85 (2H, d, J = 5.1 Hz), 3.31 - 3.45 (4H, m), 4.20 (1H, dd, J = 6.9 Hz, 10.3 Hz), 4.34 (1H, dd, J = 8.4 Hz, 10.3 Hz), 5.35 - 5.48 (1H, m), 7.55 (1H, s).

Example 320

- 15 Tert-butyl 4-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazine-1-carboxylate

Light yellow powder, yield 70%, melting point 190-191°C (decomposition).

Example 321

- 20 Preparation of tert-butyl 4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazine-1-carboxylate

A mixture of 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl methane-
25 sulfonate (2 g, 6.6 mmol), tert-butyl piperazine-1-carboxylate (1.4 g, 7.5 mmol), triethylamine (1.3 g, 12.85 mmol), potassium iodide (1.8 g, 10.8 mmol) and DMF (15 ml) was stirred at 60°C overnight. The reaction

mixture was allowed to return to room temperature and then added water, and the resulting solution was extracted with ethyl acetate three times. The organic phases were combined, washed with water twice and then
5 with a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford tert-butyl 4-[3-(2-
10 methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazine-1-carboxylate (1.9 g, yield 73%) as a white powder.
Melting point 166-167°C.

Example 322

15 Preparation of 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride

2-(4-Tert-butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
20 b]oxazole prepared in Example 306 (1.19 g, 3.24 mmol) was dissolved in trifluoroacetic acid (30 ml) followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (30
25 ml) and added a solution of hydrogen chloride in ethyl acetate slowly followed by stirring for 30 minutes with cooling on ice-bath. The precipitates were filtered off to afford 2-methyl-6-nitro-2-(piperazin-1-

ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole
dihydrochloride (1.06 g, yield 96%) as a yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.68 (3H, s), 3.00 - 3.59 (6H, m), 4.14 (1H, d, J =
5 11.1 Hz), 4.36 (1H, d, J = 11.1 Hz), 4.50 - 6.12 (4H,
br), 8.17 (1H, s), 9.62 (2H, br).

Example 323

Preparation of 2-[4-(biphenyl-4-ylmethyl)piperazin-1-
ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

10 A mixture of tert-butyl 4-(6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-
carboxylate prepared in Example 319 (400 mg, 1.13 mmol)
and trifluoroacetic acid (10 ml) was stirred at room
temperature for 4 hours. The reaction mixture was
15 concentrated. The residue was dissolved in methylene
chloride (10 ml) and neutralized with triethylamine (2
ml, 14.35 mmol). The resulting solution was
concentrated under reduced pressure, and the residue
was dissolved in methanol (10 ml). To the solution, 4-
20 phenylbenzaldehyde (515 mg, 2.83 mmol), sodium
cyanotrihydroborate (214 mg, 3.41 mmol) and acetic acid
(0.21 mg, 3.67 mmol) were added in this order followed
by stirring at room temperature overnight. The
reaction mixture was concentrated. To the residue,
25 water was added, and the solution was extracted with
methylene chloride twice. The organic phases were
combined, washed with a saturated sodium hydrogen-
carbonate solution and a saturated saline solution in

this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =
5 20/1) to afford 2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (188 mg, yield 40%) as a white powder.

Melting point 183-185°C (decomposition).

Using corresponding starting materials gave
10 compounds of Examples 324 to 329 in the same manner as in Example 323.

Example 324

2-{2-[4-(4-Trifluoromethylbenzyl)piperazin-1-yl]ethyl}-
2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
15 White powder, yield 36%, melting point 148-149°C.

Example 325

2-Methyl-6-nitro-2-{3-[4-(4-trifluoromethylbenzyl)-
piperazin-1-yl]propyl}-2,3-dihydroimidazo[2,1-b]oxazole
White powder, yield 57%.
20 Melting point 154-156°C.

Example 326

2-{2-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]ethyl}-2-
methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
White powder, yield 53%.
25 Melting point 181-182°C.

Example 327

2-{3-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]propyl}-2-
methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

White powder, yield 65%.

Melting point 176-178°C.

Example 328

4-(N,N-Dimethylamino)-4'-[4-(2-methyl-6-nitro-2,3-
5 dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-
ylmethyl]biphenyl

White powder, yield 68%

¹H-NMR (CDCl₃) δppm:

1.58 (3H, s), 2.36 (4H, br), 2.50 - 2.60 (2H, m), 2.54
10 (1H, d, J = 14.8 Hz), 2.67 - 2.76 (2H, m), 2.84 (1H, d,
J = 14.8 Hz), 2.99 (6H, s), 3.41 (1H, d, J = 12.9 Hz),
3.48 (1H, d, J = 12.9 Hz), 3.87 (1H, d, J = 9.7 Hz),
4.30 (1H, d, J = 9.7 Hz), 6.76 - 6.82 (2H, m), 7.25 -
7.29 (2H, m), 7.46 - 7.51 (4H, m), 7.53 (1H, s).

15 Example 329

2-Methyl-6-nitro-2-[4-(2-phenyl-1H-imidazol-4-
ylmethyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-
b]oxazole

White powder, yield 93%

20 ¹H-NMR (DMSO-d₆) δppm:

1.52 (3H, s), 2.10 - 2.64 (6H, m), 2.67 (1H, d, J =
15.4 Hz), 2.74 (1H, d, J = 15.4 Hz), 3.10 - 3.70 (4H,
br), 4.04 (1H, d, J = 10.7 Hz), 4.21 (1H, d, J = 10.7
Hz), 6.97 (1H, br), 7.27 - 7.34 (1H, m), 7.38 - 7.45
25 (2H, m), 7.88 - 7.93 (2H, m), 8.12 (1H, s).

Example 330

Preparation of 2-(3,4-dichlorophenyl)-1-[4-(2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-

piperazin-1-yl]ethanone

A mixture of 3,4-(dichlorophenyl)acetic acid (418 mg, 2.04 mmol) and thionyl chloride (3 ml) was stirred under reflux for 6 hours. The reaction mixture
5 was concentrated under reduced pressure to afford a corresponding acid chloride.

On the other hand, a mixture of 2-(4-tert-butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example
10 306 (300 mg, 0.816 mmol) and trifluoroacetic acid (6 ml) was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (10 ml) and added triethylamine (2 ml, 14.35
15 mmol). To the solution, a solution of the acid chloride obtained above in methylene chloride (5 ml) was added with cooling on ice-bath followed by stirring at room temperature for 30 minutes. The reaction mixture was washed with a saturated sodium
20 hydrogencarbonate solution, water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography
25 (methylene chloride/methanol = 100/1) to afford 2-(3,4-dichlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone (255 mg, yield 69%) as a white powder.

Melting point 189-191°C.

Using corresponding starting materials gave compounds of Examples 331 and 332 in the same manner as in Example 330.

5 Example 331

1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-(4-trifluoromethylphenyl)ethanone

Melting point 168-171.4°C.

10 Example 332

2-(3,4-Dichlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

Melting point 209-211°C.

15 Example 333

Preparation of 2-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylphenyl)acetamide

 A mixture of 2-(4-tert-butoxycarbonyl-
20 piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 (500 mg, 1.36 mmol) and trifluoroacetic acid (15 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced
25 pressure. The residue was dissolved in methylene chloride (10 ml) and added triethylamine (2 ml, 14.35 mmol). The solution was concentrated under reduced pressure, and the residue was dissolved in DMF (10 ml).

To the solution, 2-bromo-N-(4-trifluoromethylphenyl)acetamide (423 mg, 1.5 mmol), potassium carbonate (207 mg, 1.5 mmol), and sodium iodide (204 mg, 1.36 mmol) were added followed by
5 stirring at room temperature for 5 hours. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times and a saturated saline solution, dried over sodium sulfate
10 and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford 2-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylphenyl)acetamide (389 mg, yield 61%) as
15 a white powder.

¹H-NMR (CDCl₃) δppm:

1.62 (3H, s), 2.53 - 2.84 (9H, m), 2.88 (1H, d, J =
20 14.8 Hz), 3.06 (1H, d, J = 16.7 Hz), 3.14 (1H, d, J = 16.7 Hz), 3.93 (1H, d, J = 9.7 Hz), 4.30 (1H, d, J = 9.7 Hz), 7.55 (1H, s), 7.55 - 7.59 (2H, m), 7.65 - 7.71 (2H, m), 9.20 (1H, s).

Using corresponding starting materials gave
25 compounds of Examples 334 to 336 in the same manner as in Example 333.

Example 334

Ethyl [4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-